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CURRENT STUDIES ON THE EFFECTS OF CERTAIN MONO- AND POLYEPOXIDE COMPOUNDS ON THE BLOOD AND BLOOD-PRODUCING ORGANS WITH ATTACHED STUDIES, COVER SHEETS AND LETTER DATED 072678		
Chemical Category		
BUTYL GLYCIDYL ETHER		

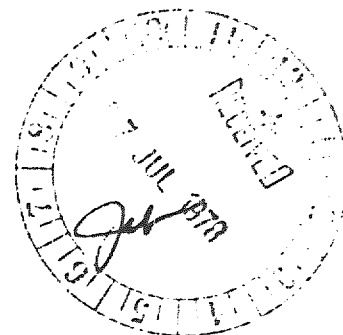
Shell Oil Company



One Shell Plaza
P.O. Box 2463
Houston, Texas 77001

July 26, 1978

Mr. Steven D. Jellinek
Assistant Administrator for
Toxic Substances
Environmental Protection Agency
Room E-637, East Tower
401 M Street, S.W.
Washington, D.C. 20460



Dear Mr. Jellinek:

BUTYL GLYCIDYL ETHER
EPA REFERENCE NO. 8EHQ-0778-0213

This letter is in response to the EPA subpoena served on Dr. M. J. Sloan in our Washington Office on July 17, 1978. The subpoena has been referred to me for response.

Under a cover letter signed July 12, 1978 by Dr. P. F. Deisler, Jr., Shell transmitted to the Director of the Office of Toxic Substances a report entitled "Chronic Vapor Toxicity of N-Butyl Glycidyl Ether", University of California report no. 270. Also transmitted were unpublished data for a bacterial mutagenic Ames test of Butyl Glycidyl Ether by C. H. Hine, one of the authors of UC report 270. We do not believe either of these reports indicate a substantial risk. This information and the cover letter were mailed from Houston on July 12, 1978 to our Washington office. The package arrived in our Washington office on July 17, 1978 and was delivered to EPA the following day.

Although UC report 270 bears a confidential notation it, and the other report were submitted for whatever use you may wish to make of it. In mid-February these reports were circulated to BGE producers or former producers for comments and background for an ongoing BGE toxicity study being conducted at the University of Texas Medical Branch at Galveston.

UC report 270 conducted in 1957, involved 50 7-hour exposures of male rats to four vapor concentrations of BGE. The concentrations were 38, 75, 150, and 300 ppm. At 38 and 75 ppm levels the authors concluded that there were no signs of toxicity. Signs of toxicity appeared at 150 ppm and increased at the 300 ppm level. Based upon the results the authors suggested a threshold exposure limit of 50 ppm.

Neither the abstract nor the summary portions of the report noted the testicular atrophy observed in 7 of the test animals detailed in the "results" section of the paper. A review of the report indicates that no specific weights of the testes were taken as was done with other body organs. No histopathological examination of tissue of the testes is indicated. Observations of atrophy probably were visual and without a baseline comparison. In the "discussion" section, the authors assume the atrophy was not a result of exposure to BGE but was rather secondary to "some other abnormality, especially pneumonia".

As a result of conversations with Dr. Marvin S. Legator of UTMB in Galveston, Shell and two other BGE producers, Ciba-Geigy and Celanese, are sponsoring mutagenic studies by UTMB which are a follow-up to earlier studies conducted by Dr. Legator and which Shell reported to the EPA on February 21, 1978. The new study will involve topical application of BGE at dosages of .375, .75, and 1.5 g/kg, and a saline control in similar quantities. A pathological evaluation will involve a gross necropsy of all control and treated animals and fixations of liver, lungs, kidney and testes tissues in Bouins and Clelland's reagent. Results of the pathological examination should be received in either October or November. Shell will advise you of the results.

The second document item requested in the subpoena requests "all other documents concerning substantial risk of injury to health or the environment of Butyl Glycidyl Ether". A review of our files does not reveal that we have any documents indicating that BGE presents a substantial risk of injury to health or the environment. Therefore, I cannot be directly responsive to your request in this category. Nevertheless, I enclose the following, which we have not submitted previously, because they are peripheral to the areas of emphasis in the earlier submissions:

1. A memorandum from C. H. Hine to T. B. Albin, dated September 4, 1956, concerning "Toxicity of Epon 815 and Epon 820".
2. A memorandum from C. H. Hine to T. B. Albin, dated July 15, 1957, concerning "Current Studies on the Effects of Certain Mono- and Polyepoxide Compounds on the Blood and Blood-Producing Organs".
3. A University of California report dated March 13, 1956, entitled "The Toxicity of Glycidol and some Glycidyl Ethers", UC Report 253.
4. A letter from C. H. Hine to Dr. N. G. White dated November 25, 1958.
5. A University of California report entitled "Skin Irritation and Toxicity of a Series of Experimental Epoxy Compounds" dated December 18, 1957, UC Report No. 275.

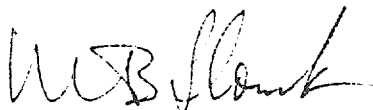
6. A memorandum from M. B. Slomka to H. Frank dated October 22, 1974 and concerning "Comparative Skin and Eye Irritation of 5 Substituted Glycidyl Ethers".
7. A memorandum from M. B. Slomka to H. Frank dated January 14, 1975 and concerning "Primary Skin Irritation Test with several lots of N-Butyl Glycidyl Ether".

Also enclosed are the results of a literature search conducted by my department. Although various of these documents submitted bear a notation of confidentiality, Shell does not wish to assert such claim to such documents.

Shell does not believe that the new information about the biological effects of BGE indicates a substantial risk. Vapor pressure is very low (2 mm at 70°F) and respiratory protection is advised; other protection is advised to prevent any skin contact.

Although the document requested in the first part of your subpoena has already been submitted, and in our opinion there are no other documents to submit under the second part of your subpoena, the enclosed packet represents the total of all documents that may be pertinent to your action. In the future, if you have need of any additional data concerning BGE please do not hesitate to write or telephone. When additional information is received, which is pertinent to BGE toxicology, it will be transmitted to you.

Yours very truly,



M. B. Slomka, Ph.D., M.D.
Consulting Toxicologist

Attachments

September 4, 1956

T. B. ALBIN

C. H. HINE

see ltr.
9-7-56
Teal 5-11TOXICITY OF EPON 815 AND EPON 820

During the week of August 13, Dr. White, Manager of Industrial Hygiene, Shell Chemical Corporation, discussed with me the problem of the toxicity and skin-irritating properties associated with EPON 815 and EPON 820. He stated that since these EPONS would be used in increasing amounts and since there was evidence from field data that they were more prone to cause dermatitis than EPON 828, an investigation should be carried out to obtain basic toxicity information. This request was formalized by his letter of August 21 to you.

From information which I have since received, the composition of EPON 815 is (10.5% n-butyl glycidyl ether, while that of EPON 820 is (89.5% EPON 828 essentially (4% glycidyl phenyl ether 96% EPON 828.

Review of toxicity reports submitted by the University of California indicates that considerable toxicity data has been accumulated on the basic components of these two EPONS. I have reviewed especially U.C. Reports 247, 233, 240 and 253 and have summarized, in Tables 1 and 2 attached, the essential information on the toxicity and irritating effects of these compounds.

While n-butyl glycidyl ether and phenyl glycidyl ether are more toxic than EPON 828 by approximately an order of magnitude, when given to experimental animals intergastroscally or applied to the skin, the toxicity class is still only that of "slight" or "practically non-toxic". The only conceivable systemic toxicity problem which might occur from use of these compounds would be associated with vapor exposure to n-butyl glycidyl ether. Here the lethal concentration for rats is 1030 ppm for a single 8-hour exposure. Chronic toxicity studies with this compound which have been completed but not yet reported indicate that continual exposure to 150 ppm or less does not produce any evidence of chronic untoward effects. However, the compound contains good warning properties. Therefore, it would appear that an evaluation of the systemic toxicity of EPON 815 and EPON 820 would probably not be necessary since it is possible to reasonably extrapolate from the available data that the toxicity is of a low order, and since the industrial hygiene practices which Dr. White has developed for the glycidyl ethers would be more than adequate for handling these two EPONS.

Reference to the data on irritating effects indicates that n-butyl glycidyl ether, phenyl glycidyl ether and EPON 828 are only

9/4/56

mildly irritating to the eye and that single or occasional contact with the skin produces no irritation with EPON 828, mild irritation with phenyl glycidyl ether, and moderate irritation with n-butyl glycidyl ether. Reference to the data on repeated application is more meaningful for the purpose of predicting the likelihood of skin irritation resulting from industrial usage of these compounds. It may be seen that while EPON 828 is only mildly irritating on repeated contact, n-butyl glycidyl ether and phenyl glycidyl ether are moderately irritating, the latter compound being somewhat more so. It can be reasonably predicted that resin formulations containing the two glycidyl ethers will be more irritating than EPON 828 and that increased caution must be observed in avoiding prolonged or repeated contact of these compounds with the skin. While it may be possible that these ethers may cause a synergistic irritating effect when in combination with EPON 828, it is unlikely that this would be of an intensity which would warrant unusual concern relative to their use. Again it would appear that practices advocated for the control of the glycidyl ethers would be sufficient to control any dermatitis which might be associated with the handling of EPON 815 and EPON 820.

9-7-56
I would suggest that the summaries of the data and my comments be forwarded to Dr. White. It may be that after reviewing these he will feel that additional toxicological studies will not be required and that he will be able to develop safe handling information with the additional data which has been furnished him.

His further comments on this matter will be appreciated.

ORIGINAL SIGNED BY

C. H. Rine, M.D.

CHH/jck
Attachments
cc: Addressee (6)

cc: R.A. Pratt

TABLE I. Summary of Toxicity Data and Toxicity Classifications) of

n-Butyl Glycidyl Ether, Phenyl Glycidyl Ether and EPOX 828

TOXICITY DATA

Compound	Route of Administration					
	Intragastric		Intraperitoneal		Respiratory	
	Mice	Rats	Mice	Rats	Mice (4 hr)	Rats (6 hr)
	LD50 Gm/Kg	LD50 Gm/Kg	LD50 Gm/Kg	LD50 Gm/Kg	LC50 ppm	LD50 Gm/Kg
BGE	1.53	2.26	0.70	1.14	1/10b)	1030
PGE	1.30	3.85			CVNTs)	CVNT
EPOX 828	15.6	11.4	4.00	2.40	CVNT	CVNT
						>22.6

TOXICITY CLASS

BGE	Slight	Practically non toxic	Slight	Practically non toxic
PGE	Slight		Non Toxic	Practically non toxic
EPOX 828	Practically non toxic	Practically non toxic	Non Toxic	Relatively harmless

- a) Classification of Hodge and Sturner.
b) 1/10 dose = LD50 value for mice not obtained at saturated vapors.
c) Concentrated ("saturated") vapors non toxic at room temperature (no deaths produced by exposures).

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TABLE II. Summary of Irritation, E₁ and Irritation Classification of

n-Butyl Glycidyl Ether, Phenyl Glycidyl Ether and EPON 828

Compound	Single Application			Repeated Application		
	Eye Draize Score	Irritation Classif.	Skin Draize Score	Irritation Classif.	Mean Draize Score	Skin High Score
BGE	9	Mild	2.8	Moderate	3.3	6
PGE	8	Mild	0.7	Mild	3.2	7
EPON 828	6	Mild	0	Non Irritating	0.5	4

Moderate

Moderate

Mild

SHELL DEVELOPMENT COMPANY

EMERYVILLE, CALIFORNIA

②

RECEIVED
JUL 16 1957

TO

T. B. ALBIN

DATE

July 15, 1957

FROM

C. H. HINE

SUBJECT

ALL INFORMATION
10 11 57
CHH
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CHH to TBACURRENT STUDIES ON THE EFFECTS OF
CERTAIN MONO- AND POLYEPOXIDE
COMPOUNDS ON THE BLOOD AND
BLOOD-PRODUCING ORGANS.

In order to consolidate material for discussion of current and contemplated studies on the above subject, I have prepared the attached outline for information of interested parties.

C. H. Hine, M.D.

CHH/jck
Attachment

Studies on the Effect of Certain Epoxy Compounds
on the Blood and Blood-Forming Organs

I. Work Completed

A. Repeated Topical Application (Three daily paintings to rats):

1. Compounds:

Diglycidyl ether	0.5 gm/kg
EPON 562	2.0, 4.0 gm/kg
Propyl glycidyl ether	1.0 gm/kg
Butyl glycidyl ether:	1.0 gm/kg

B. Repeated Vapor Exposures of Rats (4 hours daily for 3 days):

1. Compounds:

DGE:	50 ppm
BGE:	250 ppm

C. Repeated Intramuscular Administration to Rats (3 daily applications):

1. Compounds:

Allyl Glycidyl ether:	400 mgm/kg
PGE:	400 mgm/kg
Butadiene dioxide:	25 mgm/kg
DGE:	25 mgm/kg
EPON 562	100, 200 mgm/kg
EPON 828	800 mgm/kg
Glycidol:	100 mg/kg
PGE:	400 mg/kg
Propylene Glycol (control)	200 mg/kg
Triglycidyl phosphate	25 mg/kg
Vinylcyclohexene dioxide	200 mg/kg

D. Single Intramuscular Administration of Dogs:

1. Compounds:

DGE:	25 mg/kg
EPON 562:	200 mg/kg

E. Repeated (twice) Intravenous Administration of Rabbits:

1. Compounds:

DGE:	10 mg/kg
EPON 562:	50 mg/kg

II. Work in Progress

A. Single Topical Applications to Rats:

1. Compounds:

DGE: 250, 500, 1000 mg/kg
EPON 562: 2.0, 4.0, 8.0 gm/kg

B. Repeated Skin Application to Rats ($5\frac{1}{2}$ weekly for 4 weeks):

1. Compounds:

DGE: 125, 250, 500 mg/kg
EPON 562: 1.0, 2.0, 4.0 gm/kg

III. Work Contemplated

A. Repeated Vapor Exposure of Rats:

1. Compounds:

DGE 25 ppm, 7 hours daily (20 X)
EPON 562 Saturated vapor, 7 hours daily (20 X) for rats and rabbits.

B. Single Skin Application to Rabbits and Monkeys:

1. Compound:

DGE: 1.0 gm/kg
EPON 562: 4.0 gm/kg
EPON 828: 4.0 gm/kg

C. Repeated Skin Application to Rabbits and Monkeys:

1. Compounds:

DGE)
EPON 562) Daily for 20 applications; quantity to
EPON 828) be based on rat values.

D. Single and Repeated IV Infusions of DGE (25 mg/kg) and EPON 562 (200 mg/kg) in Dogs.

Table 1. Repeated Topical Application
Daily Painting of Male Rats

Compound	Dose Gm/Kg	Body Weight			WBC Counts (X103)			Fem. Marrow Nucleated Cell Count (X106)	
		Initial	Final	% Change	Initial	Final	% Change	Count	% Change*
BGE	1.0	140	157	+12.1	11.0	14.0	+27.3	204	0
DGE	0.5	118	106	-10.2	11.6	3.3	-70.0	72	-64
EPON 562	2.0	136	141	+3.7	9.3	7.9	-15.1	128	-36
EPON 562	4.0	124	114	-8.2	11.5	8.8	-23.5	85	-57
PGE	1.0	139	149	+7.2	12.6	13.4	+6.4	204	0

Table 2. Repeated Vapor Exposures to Rats
(Four Hours Daily for Three Days)

Compound	Dose Ppm	Body Weight			WBC Counts (X103)			Fem. Marrow Nucleated Cell Count (X106)	
		Initial	Final	% Change	Initial	Final	% Change	Count	% Change*
BGE	250	128	141	+10.2	15.0	8.5	-43.3	192	-4
DGE	50	145	139	-4.1	16.9	12.3	-27.2	149	-25

Table 3. Repeated Intramuscular Administration
(Series of Three Daily Doses) to Rats

Compound	Dosage Mg/Kg	No. of Series	White Blood Count			
			Initial	4 Days	8 Days	12 Days
AGE	400	1	16,000	8,400		
BGE	400	1	8,200	10,300	10,100	9,800
Butadiene Dioxide	25	2	10,700	5,700	8,800	7,700
DGE	25	2	10,700	7,200	11,500	12,000
EPON 562	100	2	11,400	9,900	11,300	11,300 ^{a)}
EPON 562	200	2	10,200	8,600	5,300	5,100 ^{b)}
EPON 828	800	1	9,700	10,300	13,300	14,500
Glycidol	100	1	13,500	13,200		
PGE	400	1	10,500	14,800	15,800	15,200
Propylene Glycol	200	2	10,300	11,100	10,400	14,200
Triglycidyl PC ₄	25	1	14,200	10,400		
Vinylcyclohexene dioxide	400	1	16,900	5,900		

a) Femoral marrow nucleated cell count: 176 X 10⁶.

b) Femoral marrow nucleated cell count: 82 X 10⁶.

Table 4. Single Intramuscular Administration to Dogs

Compound	Dose Mg/Kg	Dog	White Blood Count					
			Days Post Injection					
			-15	0	2	6	14	22
DGE	25	1	18,800	13,300	10,500	15,000	45,400	22,300
		2	12,500	5,600	20,200	10,000	16,200	16,400
		3	7,800	15,500	12,600	6,800	40,700	15,100
EPON 562	200	4	17,900	17,200	23,000	2,000	43,800	25,500
		5	11,000	9,800	9,400	2,200	11,400	14,100

Table 5. Repeated (2) Intravenous Administration, Rabbits

Compound	Dose Mg/Kg			
		0	4	8
DGE	10	9,900	8,000	11,900
EPON 562	50	5,100	5,400	8,700

PRIVATE AND
CONFIDENTIAL

3

~~CONFIDENTIAL~~ REPORT

Best Copy Available

To: Shell Development Company
4530 Horton Street
Emeryville, California

From: Department of Pharmacology and Experimental Therapeutics
University of California School of Medicine, San Francisco

The Toxicology of Glycidol and some Glycidyl Ethers

Vol. 1, Part 1, No. 253

Submitted by: C. H. Fine, M.D., Ph.D.
H. R. Anderson, M.D.
J. S. Wellington, M.D.
K. Kodama, M.S.
M. K. Gurlap, D.V.M.
D. W. Simonson, A.B.

13 March 1956

CONFIDENTIAL

The toxicity of glycidol and five related ethers, allyl glycidyl ether, n-butyl glycidyl ether, diglycidyl ether, isopropyl glycidyl ether, and phenyl glycidyl ether, was evaluated experimentally. α -Monochlorohydrin was included in the study, since it was purported to be a metabolic product of glycidol; experimental evidence did not substantiate this theory.

The predominant signs of toxicologic activity varied according to the route of administration: depression of the central nervous system on intragastric administration; hypoxia, aerophagia, dyspnea, and irritation of the pulmonary tract on respiratory exposure; and irritation varying from erythema to eschar on cutaneous application.

While the compounds varied somewhat in toxicity according to the route of administration, none of the compounds would be classified as more than moderately toxic on single exposure; most of them were slightly toxic or practically nontoxic.

The five ethers ranged in their irritating effects on the eye from mild (BGE and PGE) to severe (DGE). Diglycidyl ether was severely irritating to the skin on single application; on repeated application, glycidol and phenyl glycidyl ether also produced severe degrees of irritation.

Only allyl and isopropyl glycidyl ethers caused any evidence of systemic toxicity on repeated exposure to 400 ppm of vapor.

Similar to other common industrial chemicals such as ammonia, acid gases and acrolein, which possess good warning properties, the compounds offer relatively slight hazard from breathing of the vapors. Percutaneous absorption does not appear to offer any serious hazard in industrial use, because of the low toxicity by this route. All of the compounds produced skin irritation on repeated contact, and dermatitis may be expected in personnel exposed cutaneously.

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Recent studies in this laboratory have included the investigation of a number of compounds containing epoxy linkage. The toxicity of four EPON resins and diglycidyl resorcinol has been discussed in U. C. Report 240. Other studies on EPON resins and associated adducts and hardeners have been reported in U. C. Reports 227, 229, 232, 233, 236, 245, 248, and 252.

The present report is concerned with a series of glycidyl derivatives: allyl glycidyl ether (AGE), n-butyl glycidyl ether (BGE), isopropyl glycidyl ether (IGE) and phenyl glycidyl ether (PGE). Since there was a possibility that glycidol might undergo a biological transformation to α -monochlorohydrin (MCH) the comparative toxicity of this compound was also evaluated. (See letters of June 24, August 26, and September 23, 1953, and of November 10, 1955.) Diglycidyl ether (DGE), previously reported on (U. C. Report 205) is included for comparative purposes also. Structural formulas and important physical properties of these compounds are shown in Table 1.

Though glycidol is at present only of research interest, the four glycidyl ethers have industrial applications. These applications and potential uses are: as stabilizers of chlorinated hydrocarbons against deterioration, as viscosity reducers for epoxy resins, and for application as surface coatings.

An estimation of the systemic toxicity and surface-irritating effects of these compounds appeared desirable in order to evaluate the precautions necessary for their safe handling. The experimental design in these studies includes: primary irritation studies, determination of LD₅₀ values by intragastric and intraperitoneal (BGE) and cutaneous administration to rodents, single and repeated vapor exposures, and repeated cutaneous applications.

Test animals

The rats employed in these studies were males of the Long-Evans strain, obtained from the Simonsen Laboratories in Gilroy, California. Those on acute experiments were housed 5 or 6 to a cage, and fed standard laboratory pellets. Those used for long-term experiments were housed two to a cage and fed on a special green powdered diet obtained from the Simonsen Laboratories.

The mice were males of the Webster strain, obtained from the Simonsen Laboratories, except for those used in the experiments with n-butyl glycidyl ether, which were of the Princeton strain and obtained from the Hooper Foundation. They were housed and fed as were the rats used for the acute experiments.

The rabbits were California Albino or New Zealand White males, obtained from the Casa Ladrillo Rabbitry, Point Reyes, California or from the Simonsen Laboratories. They were housed singly, and fed standard rabbit pellets.

ACUTE STUDIES. In all acute experiments, the animals were held for a ten-day observation period after treatment, during which mortality records were kept and weight changes recorded. Representative survivors were then killed for necropsy: mice and rats by decapitation under light ether anesthesia and rabbits by air injection into an ear vein. Suitable tissues were taken for histologic examination from all animals sacrificed, and from those that died during laboratory hours. LD_{50} values were calculated by the method of Litchfield and Wilcoxon (1949) in most experiments; for the percutaneous studies the method of Weil (1962) was used.

A. Intragastric administration. After the approximate lethal range had been established with groups of two animals, rats and mice in groups of 5 or 6 (weighing 89 to 150 and 18 to 22 Gm., respectively) were given graded doses of the seven compounds intragastrically by means of a ball-point needle and syringe. Doses are specified in Tables 2 and 3. Glycidol and AGE were diluted to 50 per cent concentration for rats, and to 5 per cent for mice. Diglycidyl ether was given undiluted to rats and in 50 per cent concentration to mice. BGE was given undiluted to rats and in 20 per cent concentration to mice. MCH was given in 5 per cent concentration to both species. In all cases, the diluent used was propylene glycol.

B. Intraperitoneal administration. Only BGE was tested by this route. Groups of 5 rats (121 to 161 Gm.) and 5 mice (21 to 29 Gm.) were given graded doses of BGE by intraperitoneal injection (Table 4). The compound was given undiluted to rats, and 20 per cent in propylene glycol to mice.

C. Cutaneous administration. Healthy rabbits (2.0 to 2.5 Kg.) were clipped free of hair in a cylindrical swath from the shoulders to the hips, twenty-four hours before use. The undiluted compounds, in graded doses (Table 5) were introduced under rubber sleeves except in the case of diglycidyl ether. It was assumed that the amount lost by volatilization of this compound was insignificant, since the boiling point under standard conditions was relatively high (estimated as 170°C./460 mm. Hg). The sleeved rabbits were wrapped in towelling to further minimize evaporation, and held in a multiple rabbit holder (Lang, 1949) for seven hours. The diglycidyl ether rabbits were immobilized for twenty-four hours, to prevent licking of treated areas.

D. Vapor exposure. In these experiments graded concentrations of the compounds were used when death was produced with exposure to concentrated vapors. The term 'saturated' vapors is not used since it is our experience that the theoretical value is frequently not obtained. The concentrated vapors approached theoretical saturation except with DGE, where due to a small volume of sample only about 200 ppm was obtained.

1. Four-hour period. Groups of 5 or 6 mice (20 to 28 Gm.) were exposed to graded concentrations of the vapors of glycidol, AGE and IGE at $30 \pm 1^\circ\text{C}$., and to diglycidyl ether at room temperature ($25 \pm 1^\circ\text{C}$.) for four hours, in a glass chamber of 19.5 liters capacity. The motor-driven syringe assembly previously described by Hine et al. (1953) delivered measured amounts of the test compound from a 10-ml. Luer-Lok syringe into an evaporator through which metered air moved at a uniform rate. Similar groups were exposed to concentrated vapors of PGE and BGE. High concentration was obtained by bubbling air through a fritted glass disc immersed in the compound, which was held in a glass container. The rate of airflow was set at approximately 5 liters per minute, for concentrated vapors, and at 3 to 11 liters per minute for the graded concentrations. Nominal concentrations were calculated by the standard gas-concentration formula of Jacobs (1949) and were checked by determining the total quantity of material vaporized.

2. Eight hour period. Groups of 6 rats (110 to 140 Gm.) were exposed for eight hours to graded concentrations (Table 7) of glycidol, AGE, BGE, and IGE, with temperatures and apparatus as described for the four-hour vapor exposure.

Groups of 6 rats were also exposed for eight hours to concentrated vapors of MCH, DGE and PGE, at $30 \pm 1^\circ\text{C}$. The concentrated vapors were obtained as described above.

PRIMARY IRRITATION STUDIES

A. Skin Irritation. The skin-irritating properties of glycidol, AGE, BGE, diglycidyl ether, and IGE were determined by the method of Draize (1955).

The back and flanks of rabbits (2 to 3 Kg.) were clipped twenty-four hours prior to use. The shoulders and hips were used as test sites, two areas on each animal being scarified and two intact. Scarification was accomplished by making four intersecting epidermal scratches, each about 2 cm. long, with a scalpel blade. A patch consisting of three layers of gauze was secured over each area with adhesive tape, and 0.5 ml. of the undiluted compound was introduced under the gauze. The rabbits were wrapped in towels and immobilized for twenty-four hours, after which the areas were examined and irritation scores noted. A second reading was made at seventy-two hours.

B. Eye Irritation. Normal rabbit eyes were preselected on the basis of absence of grossly visible staining by a 5 per cent aqueous solution of fluorescein sodium, flushed with distilled water 20 seconds after instillation. After a two-hour interval, to allow the eyes to return to normal, a compound was instilled into one eye, leaving the other for a control. All compounds were given in the amount of 0.1 ml., undiluted. They were dropped on the center of the cornea while the lids were retracted; about one minute later the lids were released. Readings were made at one, twenty-four, and forty-eight hours, according to the method of Draize.

III CHRONIC STUDIES

Chronic studies were carried out as quantity of sample and time permitted. Glycidol and the five glycidyl ethers were applied repeatedly to the backs of rabbits. An insufficient quantity of diglycidyl ether prevented repeated vapor exposures to this compound. The effects of repeated exposure to n-butyl glycidyl ether are currently under investigation. Repeated vapor exposures were carried out at four concentrations of AGE, at 400 ppm of glycidol and IGE, and at 100 ppm (approximate saturation) of PGE.

A. Repeated application. The method employed in these tests was similar to that used in previous studies of the irritating properties of EPON curing agents (e. g. U. C. Report 232, 1955) and was based on the method of Draize (1955). The skin of the backs of rabbits was used in all studies. The hair was closely clipped from the back at least twenty hours before the tests were made. When it was necessary to clip regrowth of hair during the experiment, a period of at least fifteen hours was allowed for healing of possible injury before further applications were made. Six rabbits were used for the series.

The compounds were placed on the backs in a geometrically even pattern, and the locations were changed on successive rabbits. All applications consisted of 0.2 ml. of the test material, applied with a syringe and spread with a glass rod over an area approximately 1 cm. in diameter. The material was removed at the end of one hour by wiping with soft laboratory tissues, followed by tissues moistened with acetone.

Daily applications were made, excepting weekends, until the degree of eschar formation at the site made further applications undesirable or the animals showed signs of systemic toxicity.

B. Repeated vapor exposure. Groups of 10 rats were given 50 daily seven-hour exposures (except weekends) to 400 ppm of glycidol, AGE, or IGE, or to saturated vapors of PGE. In another experiment, groups of 10 rats were given 50 similar exposures to 260 ppm of AGE; exposures to 600 and 900 ppm of AGE were terminated at the end of 25 exposures, because of the undue toxicity. All control groups were exposed to uncontaminated air.

Exposures were made simultaneously in chambers of 200 liters capacity, and the air flow ranged from 11.7 to 22.0 liters per minute (3.5 to 8.6 air changes per hour). The constant-metering device, similar to that described under the heading of acute exposures, delivered the liquids in measured amounts to the evaporator, where it was vaporized in the air entering the chamber. The air in the chamber was allowed to equilibrate to a theoretical 95 to 99 per cent of the desired concentration before the animals were introduced.

Vapor concentrations were monitored by frequent analysis of air drawn from a sampling port and absorbed in a magnesium chloride and hydrochloric acid solution. The details of this method and its application in industrial hygiene air analysis will be summarized in a later report.

The rats were carefully observed at intervals during the exposure, and were weighed weekly. At the end of the experimental period, all survivors were decapitated under light ether anesthesia, and blood collected for hemoglobin content (Sahli method). At necropsy, the animals were carefully examined for gross pathologic changes, and the lungs, livers and kidneys of all animals were freed of connective tissue and excess moisture and weighed for determination of organ/body weight ratios. Sections of these tissues were retained for histologic examination, and also tissues from alternate animals as follows: brain, thyroid, thymus, heart, stomach, intestine, pancreas, adrenals, testis, and bladder.

Organ/body weight ratios, percentage weight gains, and hemoglobin concentrations of the experimental animals were compared with those of the control animals by the Student t test.

RESULTS

I ACUTE STUDIES

A. Intragastric administration. Mortality ratios following intragastric administration of the compounds are given in Tables 2 and 3.

Glycidol. Rats exhibited lacrimation in five or ten minutes, and slight to moderate depression and dyspnea within thirty to sixty minutes, at all dose levels except the lowest, 0.46 Gm./Kg. Within ten to forty-eight hours, all exhibited varying degrees of stimulation of the central nervous system, such as hyperactivity, hypersensitivity to sound, vibration of the whiskers, volitional tremors of the head or body, and intermittent epileptiform convulsions. Deaths occurred within four to forty-eight hours, and the LD₅₀ was 0.85 Gm./Kg.

The rats that died showed diffuse moderate to severe inflammation of the lungs with pleural effusion; hyperemia of the adrenals and gastroenteric tract, with fluid distention of the stomach; mottled discoloration of the liver and kidneys; some edema of the peritoneal fat and lymph tissue; gelatinous appearance of the pancreatic tissue; and an occasional pale spleen. Aside from the slight inflammation, ascites and punctate lesions of the lungs, the most pronounced gross pathologic change in rats sacrificed at the end of the ten-day observation period was pallor of the kidneys; these were swollen to almost twice the normal size and had a granular appearance. Tissues of 7 rats showing gross changes were examined microscopically, and all were judged normal with the exception of one case of pulmonary congestion.

Mice showed depression at all dose levels above the lowest (half the LD₅₀, or LD₄), and signs of gastric irritation even at this level. At the highest dose, 0.65 Gm./Kg., one animal became ataxic at five hours. Deaths occurred between the seventeenth and forty-eighth hours, and the LD₅₀ was 0.45 Gm./Kg.

At necropsy, the mice showed punctate hemorrhages of the lungs and hyperemia of the adrenals and the gastroenteric tract. Two animals given 0.3 Gm./Kg. appeared to have died in convulsions, since the forelimbs were adducted and the hind limbs extended. Among the mice histologically examined, three dying at the higher doses showed congested livers; one also showed a congested kidney. The specimens from all groups were otherwise normal.

α -Monochlorohydrin. Rats showed practically no evidence of toxicity during the first seven hours after administration. However, after twenty-two hours, moribund rats exhibited prostration, hypnosis, sluggishness, dyspnea, moderate lacrimation, and flaccid paralysis of the head or legs. Weight loss was apparent among the survivors during the second and third days. The previous weight was not regained, in most cases, during the subsequent days of the experiment. Dose levels ranged from the LD₇ to the LD₈₃, and the LD₅₀ was 0.10 Gm./Kg.

On necropsy, the rats that died showed moderate to severe diffuse irritation of the lungs with hemorrhagic lesions and marked pleural effusion; slight to severe irritation of the gastroenteric tract with some friable livers; slight ascites; enlarged and hyperemic adrenals; pale, swollen, granular-looking kidneys; somewhat gelatinous pancreatic tissue; and an occasional edematous condition of the lymphatic and lipoidal tissue of the peritoneum. Those sacrificed after ten days had hyperemia of the lungs,

granular kidneys. Microscopically, there was acute inflammation in the hilar fat, early necrosis of the tubular epithelium with precipitated protein in the tubules, and stages of regeneration of epithelium with dilation of tubules and presence of casts.

The mice became quiet on receiving the intragastric instillation, but resumed normal activity in about fifteen minutes. The sequence of signs preceding death was: irritation with ataxia; stretching out; grotesque postures; loss of the righting reflex; rigidity of the tail. Occasional mice showed signs of delirium, such as aimless running or convulsive movements, and some showed partial paralysis.

At all dose levels (LD_{01} to LD_{99}) gross observation showed hemorrhagic livers, adrenals, and spleens among the mice; and at the highest level the kidneys were enlarged and pale. No changes were seen in the tissues of the 2 mice examined microscopically.

Allyl glycidyl ether. Within ten minutes the rats showed signs of distress such as slight lacrimation, matted fur, restlessness, and slight unsteadiness. Slight to moderate depression and dyspnea were usually seen between fifteen and ninety minutes after administration. Aside from a slight unthrifty appearance, or slight dyspnea, most survivors recovered overnight. Animals that finally died sank into a lethargy or coma before death. At the LD_{50} , deaths occurred in four hours to five days, while at the highest dose deaths occurred in little more than two hours.

Rats that died showed moderate diffuse inflammation of the lungs, slight to moderate irritation of the gastroenteric tract with fluid distention, and petechial hemorrhages in the stomach. Spleen and kidneys were pale and discolored. One of these rats had numerous petechial hemorrhages of

No gross abnormalities were noted in mice subjected to necropsy, except stomachs distended with fluid in those given 3.2 Gm./Kg. The two dead mice examined microscopically showed in one case autolysis of the gastric mucosa, and minimal peritonitis, and in the other case, normal tissues.

C. Percutaneous absorption. Mortality ratios for the six compounds are shown in Table 5. All compounds produced edema and erythema to some degree; quantitation of the degree of irritation was not attempted.

Glycidol. The rabbits showed progressive depression, and death was apparently due to respiratory failure. The time of death was six to seventeen hours, and the LD₅₀ was 1.98 Gm./Kg. Grossly, the liver was engorged and the lungs appeared normal. The tissues of the two rabbits examined microscopically were reported to be normal.

Allyl glycidyl ether. Depression increased during the seven hours of immobilization. It was just noticeable at the lowest dose level and moderate at the two highest levels. The LD₅₀ was 2.55 Gm./Kg. Necropsy showed constricted kidneys and spleens; tissues of the two rabbits examined microscopically were normal.

n-Butyl glycidyl ether. This compound also produced depression, leading to death in one to two days at the highest levels. The LD₅₀ was 4.93 Gm./Kg. The viscera were usually normal in appearance, but one rabbit had a dark and friable liver, hyperemic lungs, and dark kidneys. Stomachs, intestines and bladders were often full. No abnormalities were reported on histologic examination.

Diglycidyl ether. The rabbit receiving the largest amount, 1.5 Gm./Kg., died between three and eighteen hours after the application. The other rabbits, when removed from the holder, were observed to have slight respiratory distress and muscular weakness. This condition proved to be temporary, and the animals returned to normal in a few days. The rabbit that died showed several mottled areas on the liver; the other organs appeared to be normal.

Isopropyl glycidyl ether. The rabbits showed depression at the two higher doses, and deaths occurred between four and seventeen hours after the application. The LD₅₀ was 9.85 Gm./Kg. The lungs of the rabbits given the two higher doses were hemorrhagic in appearance, although the tissues of the two rabbits examined histologically were reported to be normal. The fumes of the compound were decidedly irritating to the person applying the compound.

Phenyl glycidyl ether. The smallest dose to produce death was 0.89 Gm./Kg. There was progressive depression in rabbits that died, reaching a maximum at about fifteen hours. The skin was uniformly eschareotic and edematous, and the edema extended into the subcutaneous connective tissue. At necropsy, the lungs appeared congested, or pale and mottled; several livers had pale mottled areas.

D. Vapor exposure. 1. Four-hour period. Mortality ratios are shown in Table 6.

Glycidol. Within five minutes, irritation of the eyes and respiratory tract became apparent, with nasal discharge, lacrimation and salivation. Slight to moderate dyspnea and swollen eyelids developed between one and two hours. Gasping, with gaseous distention of the abdomen, was seen only at the highest level, in three to four hours. Overnight recovery was usual, except for slight dyspnea in the animals surviving 450 ppm, the LC₅₀.

Several of the mice exposed at this level tolerated side position on the following day. On stimulation, they exhibited cross-flexion of the forelegs, flexion of the hind legs, rigid tail, and occasional clonus with extension of the head. Death usually was imputable both to severe gaseous distention of the gut and to irritation of the lungs.

Aliyl and isopropyl glycidyl ethers. Mice exposed to AGE and IGE showed severe irritation of the eyes and respiratory tract, accompanied by lacrimation, salivation, nasal discharge, dyspnea, severe gasping, and gaseous distention of the abdomen. Gasping was a more prominent sign with AGE than with IGE or glycidol.

n-Butyl glycidyl ether. Early signs consisted of slight depression with lacrimation. Late in the exposure, agitation was demonstrated by leaping at the sides of the chamber. Signs of irritation were pronounced in some animals, where convulsive gasping was noted. Only one death occurred in ten animals exposed to concentrated vapor (approximately 3450 ppm). This death occurred in twenty-four hours.

Diglycidyl ether. Four-hour exposures to various concentrations of diglycidyl ether revealed that mice were visibly distressed by concentrations as low as 30 ppm. Three of six mice died within one to three days after exposure to this concentration. Mortality was 100 per cent after exposure to 50 and 100 ppm; none of the mice exposed to 10 and 20 ppm died. Slight irritation of the nose and eyes appeared at all levels; lower levels elicited slight dyspnea, and there was definite respiratory distress at 30 ppm and above.

Mice that died after exposure to any of these compounds showed moderate to severe diffuse pulmonary inflammation with hemorrhage and effusion, and frothy nasal discharge. There was mottled discoloration of the liver and kidneys; hyperemic adrenals; some hypertrophic spleens; and severe gaseous distention of the gastroenteric tract. Some corneal opacity was also evident. Necropsy after ten days showed some residual hyperemia of the lungs and occasional pale and granular-looking kidneys.

The tissues of one mouse exposed to each level of glycidol, AGE, and IGE were examined microscopically; mild emphysema was seen in those exposed to 300 and 670 ppm of glycidol, but no changes in the AGE or IGE mice although gross changes had been recorded. Two mice that died during exposure to AGE showed marked pulmonary congestion and focal inflammatory cells in the liver.

Eight-hour period. Mortality ratios following the eight-hour vapor exposure are shown in Table 7.

Glycidol. Within several minutes, slight eye and nose discharge was observed in all rats, followed by mild dyspnea in about an hour. Gasping and abdominal distention from swallowed air did not appear until the fourth to sixth hour of exposure, and were totally absent at 300 ppm, the lowest

level of exposure. Practically all of the deaths occurred within eight to twenty-four hours. Corneal opacity of one or both eyes was seen in some survivors, and almost all were somewhat dyspneic and anorexic during the next several days. Recovery to an asymptomatic state was usually apparent in survivors between the fifth and seventh days. The LC₅₀ was 580 ppm.

Rats dying after exposure showed moderate to severe diffuse inflammation and hemorrhage of the lungs, pleural effusion, emphysema, bronchopneumonia, severe gaseous distention of the gastroenteric tract, pale and mottled liver and kidneys, engorged and enlarged adrenals some hypertrophy of the spleen, and corneal opacity. Necropsy of rats sacrificed after ten days revealed slight diffuse inflammation of the lungs, emphysema, bronchopneumonia, and mottled, discolored kidneys. The only microscopic finding was pulmonary emphysema, not explainable by the pathologist.

Allyl glycidyl ether. Initial irritation of the eyes of the rats by AGE vapors produced considerable lacrimation and nasal and salivary flow. Dyspnea and gasping appeared between the first and third hours of exposure at the highest levels. The incidence of corneal opacity was greater than with glycidol. Deaths usually occurred between eight and forty-eight hours after exposure, and the LC₅₀ was 670 ppm.

Gross findings at the time of death or sacrifice were the same as with glycidol. Microscopically, two cases of pneumonia were reported, with no other abnormalities.

II PRIMARY IRRITATION STUDIES

Eye irritation. The scores obtained in the eye irritation studies are recorded in Table 8. There was a marked difference in the irritating properties of DGE and PGE in comparison with the other ethers and glycidol. These two compounds were only mildly irritating, while a severe degree was reached with the individual scores of all four of the other compounds and three of these, glycidol, DGE and AGE, had average scores indicating them to be severely irritating. Despite the severity of primary injury, no blindness or permanent defects in the cornea, lens or iris resulted from the application.

Skin irritation. The results of single skin applications appear in Table 9. Only DGE would be considered severe after single contact. The maximum injury grade of erythema (4) was obtained in some rabbit with all compounds except PGE, however.

The personal experience of laboratory personnel working with these compounds confirmed the observation that DGE was by far the most irritating material when in contact with the skin.

SUMMARY

Toxicological investigations of glycidol, α -monochlorohydrin, allyl glycidyl ether, butyl glycidyl ether, diglycidyl ether, isopropyl glycidyl ether, and phenyl glycidyl ether gave the following results:

- A. Acute toxicity studies.
1. The LD₅₀ (Gm./Kg.) on intragastric administration to male mice were: glycidol, 0.45; MCH, 0.18; AGE, 0.39; BGE, 1.53; DGE, 0.17; IGE, 1.30; PGE, 1.40. 2. The
 2. The LD₅₀ (Gm./Kg.) on intragastric administration to male rats were: glycidol, 0.85; MCH, 0.15; AGE, 4.20; BGE, 2.28; DGE, 0.45; IGE, 4.20; PGE, 3.85.
 3. On intraperitoneal administration to male rats and mice the LD₅₀ of BGE were 1.14 and 0.70 Gm./Kg. respectively.
 4. The LD₅₀ (Gm./Kg.) on cutaneous application to male rabbits were: glycidol, 1.98; AGE, 2.55; BGE, 4.33; IGE, 9.65; PGE, The ALD for DGE was 1.5 Gm./Kg.
 5. On single four-hour vapor exposure of male mice, the LC₅₀ (ppm) were: glycidol, 450; AGE, 270; BGE, 6000; DGE, 30; IGE, 1500.
 6. On single eight-hour vapor exposure of male rats, the LC₅₀ (ppm) were: glycidol, 580; AGE, 670; BGE, 1030; IGE, 1100.
 7. Eye irritation grades were: glycidol, AGE and DGE, severe; BGE and IGE, moderate; PGE, mild.
 8. Skin irritation grades were: DGE, severe; glycidol, AGE and IGE, moderate; BGE and PGE, mild.

B. Chronic studies. 1. On repeated application to the skin of rabbits, DGE, glycidol, and PGE caused severe irritation; AGE and BGE moderate irritation; IGE slight irritation.

2. Exposure of rats repeatedly to the vapors indicates that glycidol at 400 ppm and saturated vapor of PGE cause no indication of untoward effect. IGE at 400 ppm and AGE at concentrations as low as 260 ppm produce evidence of chronic intoxication.

C. Comparative toxicity. The toxicity classification depends on the route of administration, and varies from moderate to practically nontoxic.

2. These compounds were briefly compared with related epoxy compounds studied by Smyth et al. (1941, 1948, 1954).

D. Safe handling. Safe handling procedures are discussed. The only practical hazards apparent are dermatitis and eye irritation.

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Table 1. Relevant Physical Characteristics of Test Compounds

Compound	Abbreviation used in this Report	Structural Formula	Molecular Weight	Specific Gravity	Boiling Point at 760 mm. Hg	Vapor Pressure at 25°C.	Theoretical d Concentration at 25°C., ppm	Water Solubility % w/v	Ppm in 1 mg./L.
Glycidol		<chem>OCC1CO1</chem>	74.05	1.115b	180	0.9	1184	completely	330
α-Mono-chlorohydrin	MCE	<chem>ClCC1CO1</chem>	110.54	1.3181c	218	0.03	40	completely	221.8
allyl glycidyl ether	AGE	<chem>C=CC1CO1CC2CO2</chem>	114.14	0.9638b	153.9	4.7	6181	14.7	214.5
n-Butyl glycidyl ether	BGE	<chem>CCCC1CO1CC2CO2</chem>	130.21	0.9087c	164	3.2	4211	2.0	188.1
Diglycidyl ether	DGE	<chem>OCC1CO1CC2CO2CC3CO3</chem>	180.16	1.1262c	170	2.4	3153	completely	188.1
Isopropyl glycidyl ether	IGE	<chem>CC(C)CC1CO1CC2CO2</chem>	116.16	0.9186b	137	9.4	1237a	18.8	210.8
Phenyl glycidyl ether	PGE	<chem>c1ccc(cc1)OCC2CO2</chem>	150.17	1.1092b	243.4	0.1	132	0.24	163.0

a Approximation from vapor-pressure curve of compound type

b Measured at 20/4

c Measured at 25/4

Table 5. Percutaneous Toxicity to Male Rabbits

Compound	Dose (Gm./Kg.)	Mortality		LD50 (Gm./Kg.)
		Ratio	Time of Death	
Glycidol	0.84 1.80 3.34 6.69	1/3 0/3 3/3 3/3	17 hours 5-17 hours 5-7 hours	1.98 (1.18-3.33)
AGE	0.73 1.45 2.9 5.8	0/3 0/3 2/3 3/3	7 hours 5.5 - 7 hours	2.55 (1.41-5.71)
BGE	2.0 4.0 8.0 16.0	0/5 1/5 5/5 5/5	3 days 1 day less than 1 day	4.93 (3.73-6.50)
DGE	0.7 1.0 1.5	0/1 0/1 1/1	18 hours	1.5 (ALD)
SE	2.76 5.51 11.0 22.0	0/3 0/3 2/3 3/3	4.5 - 7 hours 7-17 hours	9.65 (4.3-21.6)
PGE	0.89 1.78 3.56 7.10	1/3 0/3 2/3 3/3	5 days 5 days 26-48 hours	2.99 (1.47-6.10)

Table 8. Primary Irritation of Rabbit Eyes

Compound	Score at (Hours)			High Score	Average ^a Score	Irritation Class ^b
	1	24	48			
Glycidol	43 64 55	62 61 106	55 79 83	106	63	Severe
AGE	56 58 96	62 90 70	80 36 53	96	72	Severe
BGE	9 7 7	7 2 2	2 0 2	9	9	Mild
DGE	65 53 56	57 57 74	103 104 34	103	74	Severe
IGE	31 9 13	66 90 13	46 86 9	90	40	Moderate
PGE	11 9 7	7 9 9	7 7 5	11	8	Mild

^a Average of 1, 24, and 48 hour readings

^b Based on grading: 0-30 = mild
31-60 = moderate
60 = severe

Compound	Area	24 Hours		72 Hours		Combined Average	Class
		Erythema	Edema	Erythema	Edema		
Glycido:	Scarified	3	2	4	1	4.5	Moderate
		3	2				
		3	3				
	Intact	3	2	2	0		
		3	2				
		3	4				
AGE	Scarified	2	1	3	2	4.0	Moderate
		4	1	4	4		
		1	3	2	4		
	Intact	1	4	2	2		
		3	0	0	0		
		1	3	1	2		
BGE	Scarified	4	2	4	1	2.8	Moderate
		3	1	2	0		
		4	2	4	1		
	Intact	3	0	0	0		
		1	0	0	0		
		1	0	0	0		
DGE	Scarified	4	4	4	3	7.6	Severe
		4	4	4	4		
		4	4	4	4		
	Intact	3	4	3	2		
		4	4	4	4		
		4	4	4	4		
IGE	Scarified	4	2	3	6	4.3	Moderate
		2	2	3	4		
		4	2	4	0		
	Intact	2	1	1	0		
		2	1	1	0		
		1	2	3	2		
PGE	Scarified	1	0	1	1	0.7	Mild
		1	0	1	2		
		1	0	0	0		
	Intact	0	0	0	0		
		0	0	0	0		
		0	0	1	1		

Scored by the method of Draize (1955): below 2 is considered mild, over 6 is considered severe.

Table 10. Results of Repeated Application to Skin of Male Albino Rabbits

Compound	Applica- tion No.	Rabbit No.								Combined High Score	Final Mean Score
		1	2	3	4	5	6				
Glycidol	1	1 0	1 0	0 0	1 0	0 0	1 0			7	5.7
	2	3 0	3 0	1 0	2 2	1 0	3 1				
	3	4 1	3 1	4 2	3 2	1 0	4 3				
	4	4 1	3 1	4 3	3 2	3 2	3 1				
	5	4 1	3 1	4 3	3 2	4 2	3 1				
	6	4 1	3 1		3 2	4 2	3 1				
	7	4 1	3 1		4 3	4 2	4 1				
AGE	1	0 0	1 0	0 0	0 0	0 0	0 0			6	3.8
	2	1 0	1 0	0 0	0 0	0 0	0 0				
	3	0 0	3 1	0 0	1 0	0 0	0 0				
	4	1 0	3 1	1 0	1 0	3 1	1 0				
	5	2 0	3 0	2 2	2 0	3 1	1 0				
	6	2 1	3 0	3 2	2 0	4 2	3 0				
	7	2 2	3 1	3 1	2 0	4 2	3 0				
BGE	1	0 0	0 0	0 0	0 0	0 0	0 0			5	3.3
	2	0 0	0 0	1 0	1 0	0 0	0 0				
	3	0 0	0 0	0 0	1 0	0 0	1 0				
	4	1 0	2 0	1 0	2 0	3 1	2 0				
	5	2 0	2 0	2 2	2 0	3 2	3 1				
	6	2 0	2 0	2 3	2 0	4 2	3 1				
	7	2 1	1 0	2 3	2 0		3 2				
DGE	1	1 0	1 0	0 0	0 0	0 0	1 0			6	3.5
	2	2 0	3 0	1 0	1 1	1 0	0 0				
	3	2 0	4 0	1 0	1 1	1 0	1 0				
	4	4 1	4 1	2 0	4 2	3 3	4 3				
	5	4 0	4 3	3 2	1 3	4 3	4 1				
	6	4 1		4 3		4 4	4 1				
	7						4 1				
IGE	1	1 0	0 0	0 0	0 0	0 0	0 0			5	2.2
	2	2 0	0 0	1 0	0 0	1 0	0 0				
	3	2 0	0 0	0 0	0 0	0 0	1 0				
	4	1 0	1 0	3 0	1 0	3 1	2 0				
	5	1 0	2 0	3 2	1 0	2 0	3 0				
	6	1 0	1 0	3 1	1 0	2 1	2 0				
	7	1 0	1 0	3 1	1 0	2 1	2 0				
PGE	1	0 0	1 0	0 0	0 1	0 0	0 0			7	6.3
	2	1 0	0 0	1 0	0 0	0 0	2 0				
	3	1 0	4 1	1 0	3 1	1 0	1 0				
	4	2 0	4 1	2 0	2 0	3 2	3 1				
	5	3 1	4 1	3 2	2 1	3 2	3 1				
	6	3 1	4 1	3 2	3 1	4 3	3 1				
	7	4 2		3 3	3 1	4 2	3 2				

Column a refers to erythema, column b to edema. Scored according to the method of Erdine (1955)

- Glycidol: Toxicity of
- Glycidol ethers: Toxicity of
- 1,2-Propanediol, 3-chloro-: Toxicity of

TITLE

THE TOXICOLOGY OF GLYCIDOL AND SOME GLYCIDYL ETHERS

-determination of the systemic toxicity and surface-irritating effects of glycidol, mono-chlorohydrin, and five related ethers (allyl, n-butyl, di-, isopropyl, and phenyl glycidyl ethers), including skin and eye irritation, LD₅₀ values by intragastric, intraperitoneal, and cutaneous administrations to rodents, single and repeated vapor exposures, and repeated cutaneous applications to rabbits
-test animals and procedures, discussion of results (necropsy, histologic examination, mortality ratios, etc.)

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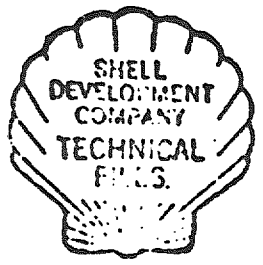
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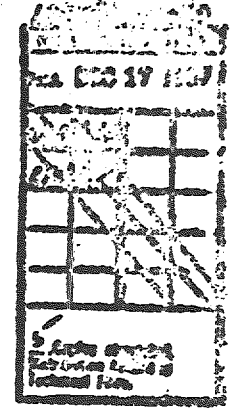
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CONFIDENTIAL REPORT



To: Shell Development Company
Emeryville, California

From: Department of Pharmacology and Experimental Therapeutics
University of California School of Medicine, San Francisco

Skin Irritation and Toxicity of a Series of
Experimental Epoxy Compounds

Submitted by: C. E. Hise, M. D., Ph. D.
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ABSTRACT

A number of epoxy compounds were tested for acute toxicity and chronic irritation. Butadiene diepoxide was moderately toxic to rats intragastrically and highly toxic on vapor exposure. Vinylcyclohexane diepoxide was slightly toxic intragastrically and moderately toxic on vapor exposure. Diglycidyl ether was slightly toxic to rabbits parentally, and on vapor exposure was moderately toxic to rats and highly toxic to mice. Poly(allyl glycidyl ether) was slightly toxic to rats intragastrically, while resin X-131 was apparently harmless at 8.0 Gm./Kg.

On chronic skin application, the following compounds were severely to extremely irritating: butadiene diepoxide, vinylcyclohexane diepoxide, diglycidyl ether, EPOX 823 containing 15 per cent diglycidyl ether, glycidylphenyl and diglycidylphenyl glycidyl ethers, and poly(allyl glycidyl ether).

n-Butyl glycidyl ether and diglycidyl resorcinol ether would be classed as moderate to severe irritants; EPOX 823 containing 8.5 per cent diglycidyl ether was moderately irritant; EPOX 823 itself and resin X-131 were mild to moderate, and bisphenol methane diglycidyl ether would be classed as mild.

Cases of apparent recession of irritation occurring while application of moderate to severe irritants were still being continued may be attributed to the formation of scar tissue.

INTRODUCTION

The Shell Development Company requested (February, 1957) that a number of new experimental epoxy compounds be included in our study of this series, and that additional information be obtained on some compounds previously tested. The new compounds were o,o'-diglycidylphenyl glycidyl ether, bisphenol methane diglycidyl ether, Resin X-131, butadiene diepoxide, and vinylcyclohexene diepoxide. It was decided to determine the acute toxicity of these compounds by intragastric administration to rats, and in the case of the two diepoxides by four-hour vapor exposure as well. All of the compounds were applied repeatedly to the backs of rabbits to assess their irritant properties.

Results previously obtained on compounds tested with this group were as follows:

Diglycidyl ether had been found severely irritant to skin and eyes of rabbits on single application, and to rabbit skin on repeated application. The intragastric LD₅₀ for rats and mice respectively were 0.45 and 0.17 Gm./Kg., and the ALD on application to rabbit skin was 1.5 Gm./Kg. The LC₅₀ for four-hour exposure of mice was 30 ppm, while rats withstood saturated vapors (estimated to be approximately 200 ppm) for this period of time without apparent ill effect (U. C. Report 803 and Hine et al., 1955). In the present experiment, four-hour and eight-hour LC₅₀ were determined by vapor exposure of rats and mice; and repeated applications were made to the backs of rabbits.

Diglycidyl resorcinol had been applied in a dose of 6 ml./Kg. to the backs of two rabbits (U. C. Report 102) with no apparent effect until after 48 hours had elapsed. The rabbits then showed depression; the skin became leathery in appearance, and both died before the tenth day. Later (U. C. Report 240), seven applications were made to the backs of rabbits with severe local effect. Three of the four rabbits died of bronchopneumonia at that point, terminating the experiment. On single application the substance was severely irritant to the eyes of rabbits and moderately

EXPERIMENTAL METHOD

1. Acute Toxicity Studies

In all of the acute toxicity studies, the LD₅₀ and LC₅₀ values were calculated by the method of Litchfield and Wilcoxon (1949). Animals that died were subjected to necropsy when feasible, and survivors were killed for necropsy at the end of the ten-day observation period. Gross examinations were made in all cases, and sections of suitable tissues of selected animals were preserved in 10 per cent formalin for microscopic study.

Intragastric administration. Butadiene dioxide, vinylcyclohexene dioxide, poly(allyl glycidyl ether), o,o'-diglycidylphenyl glycidyl ether, and Resin X-131 were given to groups of five rats (140-160 Gm.) of the Long-Evans strain intragastrically, in graded doses, by means of a ball-point needle and syringe. The solid, X-131, was difficult to administer. It was finely ground and passed through a 100-mesh sieve, after which it was suspended in distilled water (20% w/v). The rats were carefully observed for several hours after the instillation, and were examined at least twice daily during the succeeding ten days.

Cutaneous application. Graded quantities of undiluted diglycidyl ether were applied to the clipped backs of groups of five male rats (99-116 Gm.) of the Long-Evans strain, and groups of four male rabbits (1.70-3.06 Kg.) of the New Zealand strain. The fluid was spread over the backs as widely as possible with a glass rod, after which the rabbits were wrapped in rubber dam and travelling before being returned to their cages. No attempt was made to wrap the rats. The animals were carefully observed for the next several hours, and daily for the next ten days. The rabbits exposed to 1 ml./Kg. were bled before the application, and one and two weeks later, for determination of hemoglobin concentration and leukocyte counts.

Vapor exposure. Groups of 5 male rats (120-140 Gm.) of the Long-Evans strain were exposed for four hours to graded concentrations of the vapor of butadiene diepoxide and vinylcyclohexene diepoxide. Groups of 6 rats (120-170 Gm.) and 6 mice (18-28 Gm.) of the Webster strain were exposed for four and eight hours to graded concentrations of diglycidyl ether. The animals were under observation while in the chamber, and for several hours thereafter. For the succeeding ten days they were examined daily.

II Repeated Skin Applications

The compounds were tested in two groups, by a method differing slightly from that used in previous studies: the compounds were applied in transverse stripes across the back, and the areas were shaved with an electric razor after clipping, to remove all fur and permit complete removal of compounds at the end of the designated time. The areas were shaved as often as necessary to keep them free of fur during the course of the experiment.

The first group of compounds comprised butadiene diepoxide, vinylcyclohexene diepoxide, diglycidyl ether, poly(allyl glycidyl ether), glycidylphenyl glycidyl ether, diglycidylphenyl glycidyl ether, and Resin X-131. For comparative purposes, n-butyl glycidyl ether (BGE), EPON 828, and EPON 828 containing 2.5 and 15 per cent diglycidyl ether (w/w) were used. Nine male rabbits (1.5-2.55 Kg.) of the New Zealand strain were clipped over the back and sides, and then shaved. The following day the backs were again shaved, and were marked with a ball-point pen into six crosswise stripes on eight animals, and seven on the ninth. The eleven compounds, each diluted 50% w/w with acetone, were applied with sable brushes serially, beginning at the neck of rabbit 1 and ending at the rump of rabbit 9. Each compound was thus applied five times. At the end of seven hours, the compounds were all washed off with acetone and cellulose tissue, and the portions of the dividing lines that had been erased were replaced with the ball-point pen.

Applications were made five days a week until scar formation was complete, or for a total of 20, and the degree of irritation was recorded just previous to each application, using an arbitrary scale of 0. It was usually necessary to use the electric razor before application, to remove new hair growth. The rabbits were weighed weekly and were sacrificed at the end of the experimental period for necropsy. Samples of skin from each treated area, and sections of visceral organs of each rabbit, were preserved in 10 per cent formalin for histologic study.

In the second series of applications, six rabbits were used, with five shaved areas on each back. Resorcinol diglycidyl ether and bisphenolmethane diglycidyl ether were each applied to two areas, while EPON 828 was applied to the fifth. One area painted with each of the test compounds was washed off with acetone after one hour; the other three areas were washed after seven hours. Otherwise, the experiment was conducted in the same manner as the previous series.

RESULTS

I. Acute Toxicity Studies

The results of the acute toxicity studies are summarized in Table I, a and b.

At the highest level of vinylcyclohexene diepoxide (4 Gm./Kg.), the rats showed an unsteady gait within an hour, and then lapsed into coma. Slight lacrimation was present. At the two high levels, deaths occurred in two to four hours, and the rats showed lung congestion and a dull brown color of the liver. At 8 Gm./Kg. there were two deaths, one at two hours and one at twenty-four. The liver of the latter animal had whitish areas. The only gross finding in animals sacrificed at ten days was a slightly swollen appearance of the liver.

Signs shown at the highest dose of bupadiene diepoxide (0.15 Gm./Kg.) were the same as those noted with vinylcyclohexene diepoxide, but gross lesions differed somewhat. The livers were yellow, and the intestines had a blackish appearance.

One of these rats had also petechiae on the stomach, while the liver showed areas of massive damage with a sharp line of demarcation adjacent to the stomach. Not much change was seen in rats sacrificed after ten days. One showed atrophy of the thymus, and the stomachs of all others were full of white, caseous material.

With poly(allyl glycidyl ether) the signs were similar to those with vinyl-cyclohexene diepoxide at high levels. Livers and lungs were again congested in animals that died, while those sacrificed at ten days were within normal limits.

At the highest dose of diglycidylphenyl diglycidyl ether (4.8 Gm./Kg.), the rats became sluggish in ten minutes, and in twenty minutes four of the five tolerated side position. After an hour there was noticeable vasodilation, and occasional tremors of the entire body. Four of the five died within twelve hours, showing congested lungs, and a bleached appearance of the intestines.

The highest dose of Resin X-131 that it was feasible to give (8.9 Gm./Kg.) caused no toxic manifestations.

Percutaneous absorption of diglycidyl ether. The LD₅₀ was the same in both species, 1 Gm./Kg. In rats, there was depression but no apparent necrosis an hour after the application of the highest dose, 2 Gm./Kg. Two of these rats were dead the next morning, and a third died about thirty hours after the administration. The last animal in the group died on the eleventh day. All of these animals remained essentially normal in appearance and behavior until they were found dead, except that the last to die lost considerable weight, dropping from an original 113 Gm. to 60 Gm. on the tenth day.

Among the other groups, there were only two deaths, one in the group given 1 Gm./Kg. and one in the group given 0.6 Gm./Kg. No signs of overt toxic effect were noted. At necropsy, one animal given 0.25 Gm./Kg. showed areas of atelectasis in two lobes of the lungs, and one in the group given 0.6 Gm./Kg. had a blotchy liver and yellow discoloration in the small intestines. The skin was leathery in appearance in the treated areas.

Among the rabbits, the only sign of physiologic disturbance noted was polyuria, which occurred transiently at half an hour to an hour after the application. All of the rabbits given 1.5 Gm./Kg. died within 24 hours, while two of those given 2 Gm./Kg. died within 24 hours and the other two survived for the entire observation period of eleven days. Animals that subsequently died were frequently found sitting with their front feet in their water jars in a comatose condition; that they were not in a hypnotic state was evidenced by their quick reactions, jumping back when disturbed. The eyelids of these animals were occasionally adherent. Rabbits that survived usually lost weight, becoming pinched looking, and their muzzles were often discolored, probably from licking at their backs.

The backs of the animals were indurated by the morning after the application, but did not resemble the areas treated in the irritation experiment. Discoloration was sometimes purplish, sometimes yellowish to greenish, but the blackening noted on repeated application did not appear. There was no sloughing. Five of the rabbits showed an apparent edema of the belly two days after the application, which progressed to a subcutaneous necrosis. In four cases the abscess broke through the skin and drained for the remainder of the observation period; in the fourth case, the skin appeared to be unbroken.

At necropsy, the two rabbits given 2 Gm./Kg. had no apparent lesions in the viscera, although the kidneys of one appeared somewhat flabby. On the belly of one, the skin was adherent to the muscle, and an irregular area of necrosis 4 to 5 cm. across apparently invaded the muscle layers very deeply. Similar areas were found in one of the three survivors given 0.5 Gm./Kg. Another animal had about 200 ml. of clear straw-colored fluid in the peritoneal cavity, and what appeared to be multiple abscesses of the liver. The kidneys also showed purplish discolorations. All three of the rabbits given 1 Gm./Kg. seemed to have multiple abscesses of the liver, and petechiae or diffuse hemorrhages on the kidneys. The gall bladders were full, and one was very much distended.

Blood studies. The group of rabbits given 1 Gm./Kg. of diglycidyl ether by cutaneous application were bled just before the application, and one and two weeks later.

The decrease in hemoglobin amounted to only one or two grams, but because of the lack of internal variation was significant to the same degree as the drop in leukocytes, when the t test was applied ($P = < 0.001$) at the one-week interval. The individual readings were as follows:

	Weeks					
	0		1		2	
	WBC	Hb	WBC	Hb	WBC	Hb
Rabbit No. 1	8550	13.5	4100	12.1	9900	12.5
No. 2	8400	13.0	1950	11.0	(dead)	
No. 3	7550	13.0	4250	12.0	4700	12.0
No. 4	8250	13.0	5150	11.5	5800	12.0

Vapor toxicity. Rats exposed for two hours to 200 ppm of butadiene diisocyanate showed peripheral vasodilation, slight nasal discharge, and labored breathing. By the end of four hours 4 rats were dead, and the lone survivor showed copious nasal discharge, diaphragmatic breathing, lacrimation, and clouding of the corneas. On gross examination, gaseous dilation of the enteric tract was noted, and livers were mottled with areas of hyperemia.

By the end of the four-hour exposure to 133 ppm, all rats were lacrimating and their corneas were clouded. Some showed diaphragmatic breathing. One of the survivors lost weight severely (143 to 23 Gm.) during the ten-day observation period and on necropsy showed an atrophied thymus and small spleen. The other survivor gained weight normally and showed no gross lesions.

Even at 89 ppm the corneas of the rats became dull during the four-hour exposure. The rat that died at 24 hours was examined grossly and found to have congested lungs, with two lobes collapsed, and a bright red liver with exaggerated lobular pattern. Those dying at three and six days showed only slight atrophy of the thymus and spleen. At 50 ppm the effects were similar.

At 2000 ppm of vinylcyclohexene diepoxide, some vasodilation and an untoward gait were noted during the four-hour exposure. All of the rats died in the chamber or within an hour after removal. Their livers and lungs were congested. The signs noted and the gross lesions were almost identical at 1333 ppm, none of the rats surviving more than two hours after removal from the chamber.

At 890 ppm, three rats died within three hours after removal from the chamber, but two survived for the ten-day observation period. One gained normally in weight, and on necropsy showed only atrophied testes with white striations. The other gained only 2 Gm. in ten days, and its liver was pale, a yellowish brown color; its testes were striated.

At 590 and 320 ppm, there were no deaths, no definite signs of toxicity, and no gross lesions.

Exposure of mice and rats to the vapors of diglycidyl ether had few immediate effects. There was some nasal discharge, and less eye discharge. The rats tended to huddle, while mice remained active. Animals were often nearly normal when removed from the chamber, but within 24 hours would show depression, cloudy corneas, increased nasal discharge, closed eyes, swollen paws. Dyspnea was noted only in rats exposed to 113 ppm or more, and appeared after eight hours of exposure. There appeared to be a local effect on peripheral blood vessels, perhaps due to contact of the skin with the vapor, since the ears of some rats dried up and fell off in about three days, while the skin of the feet tended to slough after about two weeks.

The usual findings at necropsy included congested lungs, somewhat granular and discolored yellowish livers, enlarged kidneys, and occasionally prominent adrenals of whitish color.

Repeated Skin Applications

First series (Table 3, Figure 1). At the time of removal of the first application, the skin painted with diglycidyl ether had swollen as high as 0.5 cm. without any evidence of erythema. The same type of swelling, but not so severe, had occurred with the five streaks of butadiene diepoxide and two of the streaks of vinylcyclohexane diepoxide. EPON 828 containing 15 per cent diglycidyl ether caused severe swelling on three animals, with ecchymoses, and on a fourth, with erythema. The fifth animal showed a lumpy appearance along the streak. Glycidylphenyl glycidyl ether caused swelling on one animal, lumpiness on another, and erythema on a third. Poly(allyl glycidyl ether) and diglycidylphenyl glycidyl ether caused erythema on one animal and ecchymoses on another. Resin X-131 caused lumpiness on one animal and ecchymoses on another. Most of these effects had disappeared by the time of the first reading, just before the second application, and the appearance of either erythema or edema was very rare thereafter.

By the time of the second reading, confluent ecchymoses were scattered in bands across the backs where diglycidyl ether, butadiene diepoxide, glycidylphenyl glycidyl ether, or EPON 828 plus 15 per cent diglycidyl ether, had been applied. The effects were more severe in some animals than in others. At the time of the fifth application, rabbit 6 was found dead (a Monday morning), while rabbits 1, 2, and 5 looked very ill. These animals had apparently been licking severely irritated areas and contaminated their mouths and surrounding parts, as their muzzles were filthy with what appeared to be bloody pus. Rabbit 3 was dead the next day, and at this time applications of butadiene diepoxide, diglycidyl ether, glycidylphenyl glycidyl ether, and EPON 828 plus 15 per cent diglycidyl ether, were discontinued. Most of the areas where they had been applied now appeared as black, indurated bands in the skin. Areas painted with vinylcyclohexane diepoxide, poly(allyl glycidyl ether), diglycidylphenyl glycidyl ether, were scoring up to 7, with two to three bands of scab.

Rabbit 8 was unexpectedly found dead on the morning of the ninth application, while rabbits 1 and 5, although looking very unkempt and emaciated, survived the entire experimental period. Applications of poly(allyl glycidyl ether) were discontinued after the tenth, as the areas were all so covered with scab that penetration of the compound to the skin would have been impossible.

Scabs of the tan type were superficial in nature, and rose as hair grew beneath them. The new skin appearing was apparently less affected by the compounds than the original skin, so that the scores decreased with time. In some cases, scar tissue was obvious and hair growth was patchy. This was noted with vinylcyclohexene diepoxide, EPON 823 plus 3.5 per cent diglycidyl ether, poly(allyl glycidyl ether), and diglycidylphenyl glycidyl ether. Indurated black areas that had been painted with the four most severe compounds sometimes broke away towards the end of the experimental period (two weeks after application of these compounds had been discontinued) and scarring was always evident.

At necropsy there were no lesions noted except whitish spots on the liver, except in one animal. This rabbit showed diarrhea, with yellowish and slightly gassy ingesta. The heart appeared fatty, with an abnormal texture; the liver was discolored, and the spleen rugose.

Histologically, butadiene diepoxide had the most severe effect on the skin, which showed edema, necrosis, and focal calcification. Skin treated with diglycidyl ether showed necrosis and focal ulceration. Vinyl cyclohexene diepoxide and EGB caused necrosis and edema; coagulation necrosis and edema were noted with poly(allyl glycidyl ether), glycidylphenyl glycidyl ether, and diglycidylphenyl glycidyl ether. Resin X-131 and EPON 823 caused edema and chronic inflammation; one of the sections of EPON 823 also showed focal coagulation necrosis. The mixtures of EPON 823 and diglycidyl ether caused coagulation necrosis, edema, and chronic inflammation.

Second series. The degree of irritation during the course of the experiment is shown by numerical score in Table 4, and graphed in Figure 2. On the first application, resorcinol diglycidyl ether caused definite swelling, and erythema also appeared on four animals. After about the third application, a thin, flexible sheet seemed to form over the area, while erythema and edema were less noticeable. In some cases there appeared to be crusting, and in others a scab formed. The scabs began to break up after about the sixth application, and when they fell off, scar tissue remained. Bisphenol methane diglycidyl ether and EPOCH 638 caused very little irritation during the experimental period, although erythema and edema were occasionally present.

There was no significant difference between the readings for one-hour and seven-hour application of the compounds.

All of the rabbits remained in satisfactory health during the experimental period, and all gained weight normally.

DISCUSSION

Study of the toxicity of diglycidyl ether is hampered by the fact that the compound is not stable, and results may be expected to vary with the age of the sample. In spite of this possible variation, the test results were not too dissimilar to those reported earlier (U. C. Report 205). The percutaneous toxicity to rabbits was 1 Gm./Kg. (LD₅₀) as compared with 1.5 Gm./Kg. (AID) in the earlier test. The former LC₅₀ of 30 ppm for four-hour exposure of mice became 63 ppm, while the eight-hour LC₅₀ was 30 ppm. Contrariwise, rats were not affected by an estimated 200 ppm in the earlier experiment, while 200 ppm was the LC₅₀ in this experiment.

The effect of diglycidyl resorcinol when repeatedly applied to rabbit skin was not so severe in the present experiment as in the earlier work (U. C. Report 205). This may be due to the present use of the electric razor, which allows complete removal of the compound from the skin. In earlier experiments where only clippers were available, residual amounts of material doubtless adhered to the skin at the roots of the hair, providing essentially 24-hour contact rather than the seven-hour contact intended. On the other hand, it was noted that there was no great difference between the effects of the one-hour and seven-hour contact, and therefore the difference may be due to individual difference in the rabbits or to slight differences in the samples of diglycidyl resorcinol. The present lot was crystalline, while that used previously (LR 1029-145) was liquid.

Present experiments now under way indicate that while diglycidyl ether may be rated only as 'moderately toxic following single vapor exposure', it has a cumulative effect on repeated exposure, and should be treated with considerable caution. Full protective measures should be exerted when it is used.

Butadiene diepoxide was the most toxic of the compounds tested, falling into the 'moderately toxic' class after intragastric administration, and the 'highly toxic' class on vapor exposure. The other compounds tested were only slightly

toxic on intragastric administration, and diglycidyl ether and vinylcyclohexane diepoxide were moderately toxic on four-hour vapor exposure. Diglycidyl ether was also slightly toxic on cutaneous application.

This report contains data on skin irritation obtained by a somewhat different technic than previously used, and the method of reporting, which includes graphic representation, is felt to be a considerable aid in the understanding of the qualitative changes which occur with time. We will be happy to receive comments as to the suitability of this method.

SUMMARY

On the basis of this study, diglycidyl ether would be classified as slightly toxic percutaneously to rabbits, moderately toxic to rats on vapor exposure, and moderately to severely irritant to the skin. The compound reduced the leukocyte count and amount of hemoglobin in rabbits within a week at a cutaneous dose of 1 Gm./Kg.

Diglycidyl resorcinol ether was severely irritant to the skin on either one-hour or seven-hour repeated application.

Poly(allyl glycidyl ether) was slightly toxic to rats on intragastric administration, and severely irritating to rabbit skin on repeated application.

o-(Glycidylphenyl glycidyl ether (X-601) and o, o'-diglycidylphenyl glycidyl ether (X-801) were severely irritating to rabbit skin on repeated application, and the latter was slightly toxic to rats on intragastric administration.

Bisphenol methane diglycidyl ether was mildly irritating to rabbit skin on repeated application.

Butadiene diepoxide and vinylcyclohexane diepoxide were severely irritant to rabbit skin on repeated application. The former was moderately and the latter slightly toxic to rats intragastrically; on vapor exposure of rats, the former was highly and the latter moderately toxic.


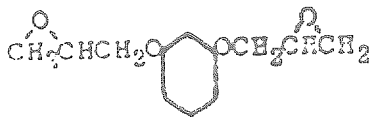



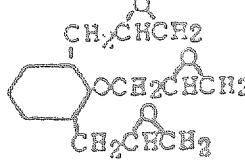


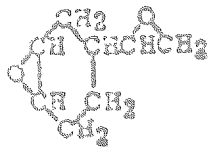
Resin X-138 was a mild to moderate irritant to rabbit skin on repeated application, and nontoxic to rats intragastrically at a level of 2.0 Gm./Kg.

n-Butyl glycidyl ether was moderately to severely irritant to rabbit skin on repeated application. EPON 828 was mildly irritant in one study, and mild to moderate in the other.

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Table 1. Description of Compounds Studied

Compound	Structural Formula	Boiling Point ^a
Diglycidyl ether (lot 4245-70)		about 230
Diglycidyl Resorcinol ether		Crystalline
Bisphenolmethane Diglycidyl ether (lot LR 3245-69)		relatively nonvolatile
Poly(allyl glycidyl ether) (lot 119820)		relatively nonvolatile
o-Glycidylphenyl Glycidyl ether (X-401-3) (lot 2047-112)		140 at <1 mm
o,o'-Diglycidylphenyl Glycidyl ether (X-401-3) (lot 2102-134)		relatively nonvolatile
Resin X-131 (Ideal formula) (lot 3907-36)		solid resin relatively nonvolatile
Butadiene Diepoxide (U.C. & C.)		158
Vinylcyclohexene Diepoxide (U.C. & C.)		227

^a °C., atmospheric pressure unless otherwise stated

Table 3. Results of Repeated Skin Applications * ~~First Series~~

Compound	Application Number																						Fish Scale	Final Mean																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																	
Diglycidyl ether	2	5	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8

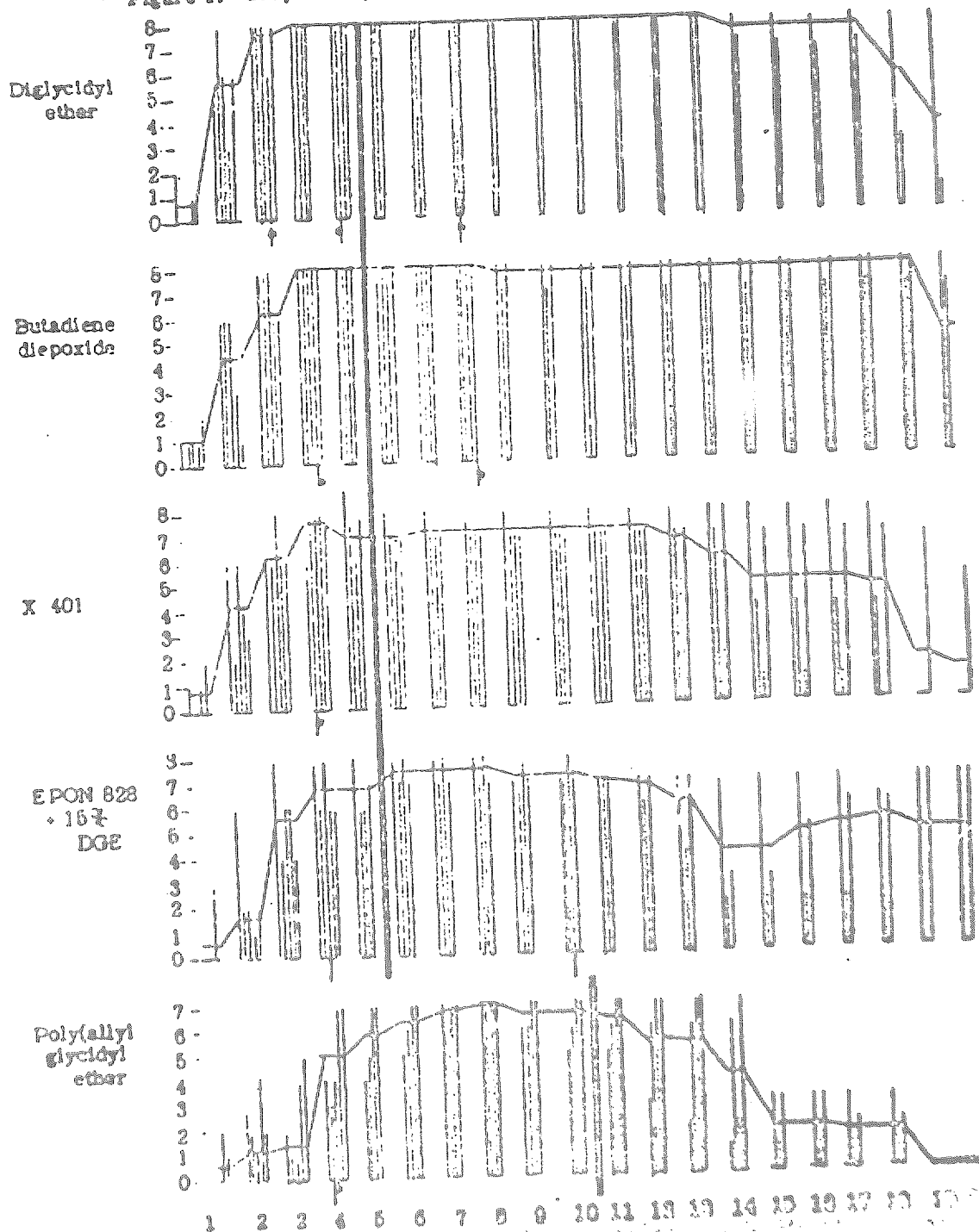
* Scored from 0 to 8 according to estimated damage. 7 = full scale 0 = full scale with apparent necrosis.

! Fear factor evident!

Table 3, concluded

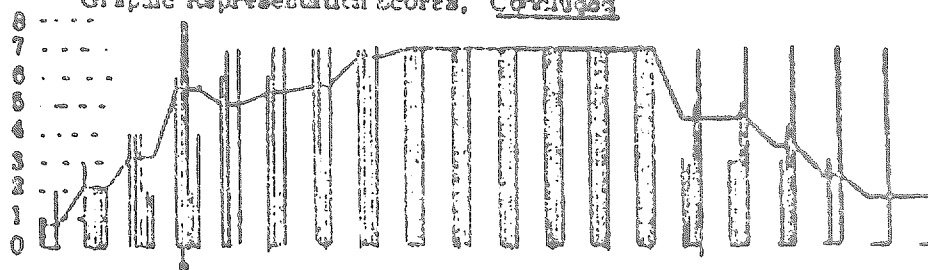
Compound	Application Number																				High Score	Final Mean Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
EPON 828 + 3.5 % DGE	0	0	1	1	1	2	2	3	3	3	3	3	2	1	1	1	1	1	1	0	(3) 2.5	1
	0	1	1	1	1	2	3	3	3	3	3	3	1	1	0	0	0	0	0	0		
	0	2	1	2																		
	2	1	1	1	2	3	3	3														
	0	0	0	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2		
EPON 828	0	0	1	1	1	1	2	2	1	1	1	0	0	0	0	0	0	0	0	0	(1) 0.9	1
	0	1	1	1	1		0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	0	0	0	1																		
	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	1	2	3	5	4		
	0	0	0	2	2	3	3	3	0	0	0	0	0	0	0	0	0	0	0	0		
Resin X-131	0	2	1	2	2	3	2	2	1	0	0	0	0	0	0	0	0	0	0	0	3 1.1 2.2 3	0.6
	0	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	0	2	3	3	3	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0		
	1	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	1	3	3	2		
	0	0	1	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1		

Figure 1. Graphic Representation of Irritation Scores



Graphic Representation Scores, Concluded

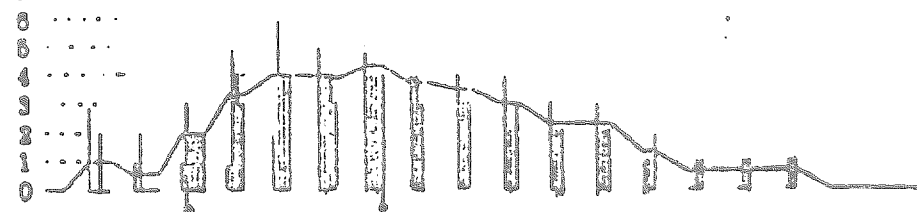
X-801



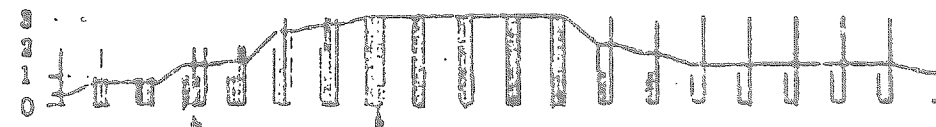
Vinyl
Cyclohexene
Diepoxide



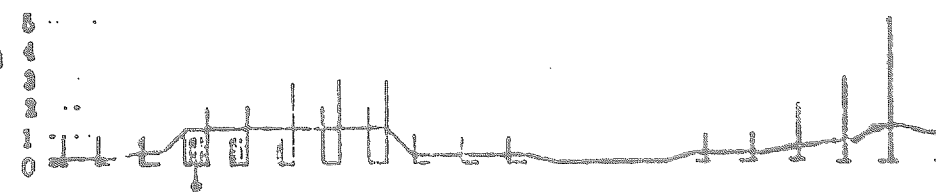
n-Butyl
Glycidyl
Ether



EPON 828
• 3.5 EDOZ



EPON 828



Resin X-151



* Animal died after this reading

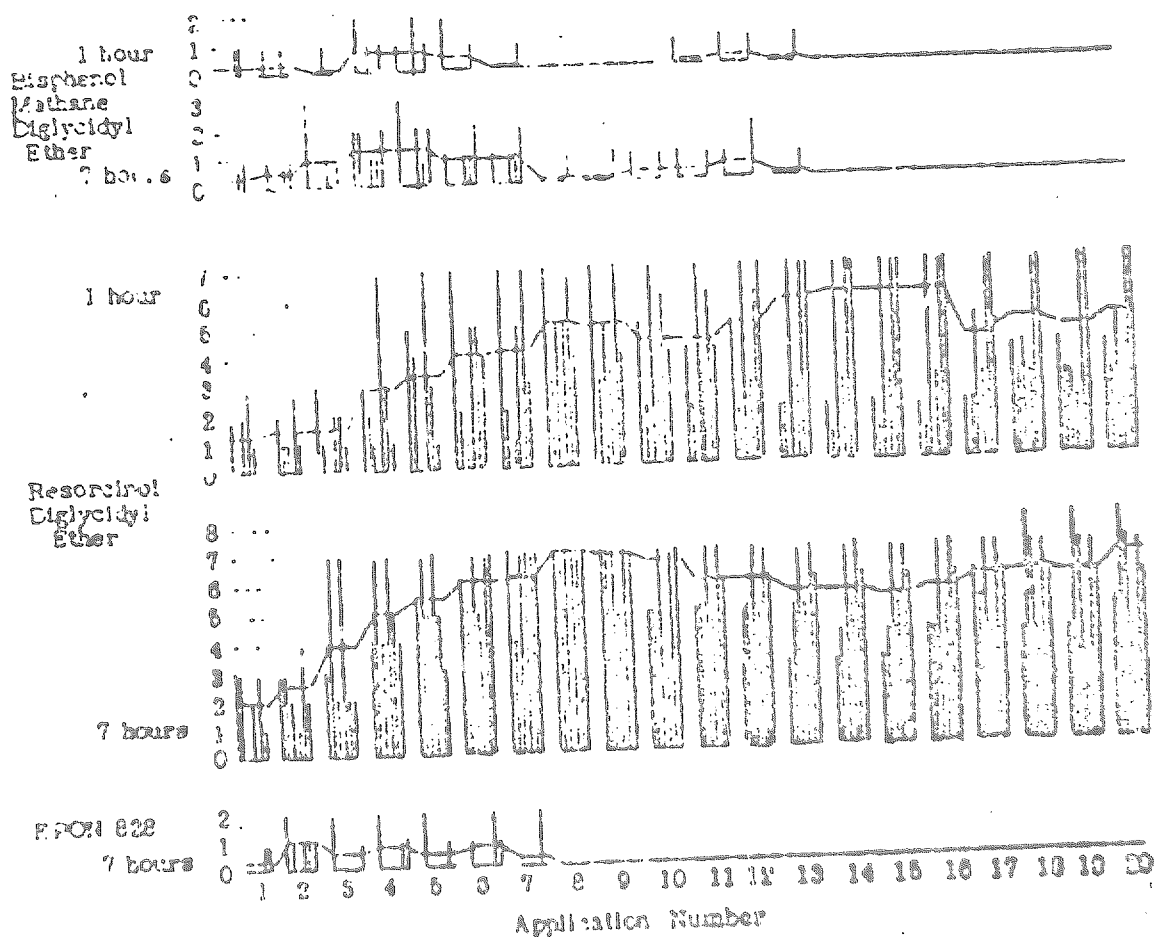
N F The heavy line indicates cessation of applications

Table 4. Results of One- and Seven-hour Applications* *Ground Squirrels*

Compound	Application Number																				Total Score	Mean Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
One hour Disphenol methane diglycidyl ether	0	0	0	0	1	2	0	0	0	0	1	1	0	0	0	0	0	0	0	0	22	0
	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	22	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	22	
	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11	
Seven hours Disphenol methane diglycidyl ether	0	0	3	2	2	1	1	0	0	1	1	1	0	0	0	0	0	0	0	0	28	0
	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	23	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	
	0	0	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	12	
One hour Resorelinol diglycidyl ether	0	0	3	3	5	7	7	7	7	5	4	5	2	2	2	2	2	2	4	4	7	0
	2	2	1	2	4	2	1	3	3	2	2	2	2	2	1	1	1	2	3	3	6	
	0	1	0	1	0	1	2	5	5	7	7	7	7	7	7	7	7	7	4	3	7	
	2	3	2	7	7	5	5	5	4	2	3	3	3	3	3	3	3	3	3	3	7	
Seven hours Resorelinol diglycidyl ether	1	1	1	1	1	4	3	4	4	4	4	7	7	7	7	7	7	7	7	7	7	23
	3	3	3	4	1	0	7	7	7	5	5	5	5	5	5	5	5	5	4	4	7	
	0	0	2	2	4	5	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	1	7	7	5	7	7	7	5	3	5	5	5	5	5	5	5	4	4	7	
EPON 828 Seven hours	0	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0
	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	
	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	
	1	1	0	1	1	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	2	
	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	
	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	
	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	

*Scored from 0 to 8 according to apparent damage; 7 = full scab, apparently superficial, 8 = full scab with apparent necrosis.

Figure 2. Graphic Representation of Irritation Scores



SHELL CHEMICAL COMPANY

6

Waterman

DATE OCTOBER 22, 1974

TO WOODBURY CHEMICAL PLANT - SENIOR
RESEARCH ENGINEER (H. FRANK)

FROM MANAGER - TOXICOLOGY &
APPLIED PHARMACOLOGY -
SAN RAMON

SUBJECT COMPARATIVE SKIN AND EYE IRRI-
TATION OF FIVE SUBSTITUTED
GLYCIDYL ETHERS

Per your request, T.A.P. has conducted eye and skin irritation studies on five substituted glycidyl ethers (see attached Table I for their names and control numbers).

These studies were contracted with the Hine Laboratories, San Francisco, Calif., and copies of the Hine reports are attached for your easy reference. (Table I identifies each laboratory report with the compound under study.)

All substances were moderate irritants to escharotics to the rabbit skin, and slight to extreme irritants to the rabbit eye. Please refer to Table I for the descriptive evaluation of each compound.

On the basis of these tests, it would appear that they should be assigned an SPI Classification rating of 5, with the exception of NEODOL[®] Detergent Alcohol Glycidyl Ether (CWLR 406-198-2), which should be classified with a 3 rating. The 5 rating, to N-Octyl Glycidyl Ether (CWLR 434-152-2), is based on its eye irritation properties.

It should be noted that these classifications are assigned in the absence of information on these compounds' sensitizing potential, if any, and on their carcinogenic potential, if any.

In a telephone discussion with Mr. Uzelmeier, he suggested that another company's Diglycidyl Ether of Neopentyl Glycol was less irritating than Shell's. If the resolution of this apparent difference is of significance, TAP would suggest a comparative double-blind, side-by-side comparison of these two materials. If such a study would be indicated, I would be pleased to discuss it with you in further detail.

May I suggest that appropriate warning labels be attached to shipping containers, and recipients of experimental supplies be appropriately warned as to hazards associated with these materials.

TAP would be pleased to receive any comments that you or your associates may have about these studies or their conduct; if you have any questions about them, please do not hesitate to contact my office.

M. B. Slomka

M. B. Slomka

Attachments

cc: Woodbury Plant - Sr. Res. Chemist (C. W. Uzelmeier) w/o attach.
Houston - Supv. Reg. Affairs - Chem. Products w/attach.
San Ramon - I.S.(2) w/o attach. ← THIS COPY FOR →

TABLE I

COMPARATIVE RABBIT SKIN AND EYE IRRITATION RATINGS FOR FIVE GLYCIDYL ETHERS

	Hine Laboratory Report Number	Skin Irritation*	Eye Irritation*	SPI Classification**
N Butyl Glycidyl Ether (CWL R-434-201)	51	Severely irritating to Escharotic (corro- sive)	Extremely irritating	5
Diglycidyl Ether of Neopentyl Glycol (CWL R-434-139)	49	Severely irritating to Escharotic	Markedly irritating	5
Diglycidyl Ether of Isobutyl Dioxitol (CWL R-434-115)	50	Escharotic (corrosive)	Extremely irritating	5
n-Octyl Glycidyl Ether (CWL R-434-152-2)	56	Moderately irritating	Extremely irritating	5
NEOBOL® Detergent Alcohol glycidyl Ether (CWL R-406-198-2)	57	Moderately irritating	Slightly irritating	3

* Relative Rankings: Escharotic or Corrosive
Severely irritating
Moderately irritating
Minimally irritating
Non-irritating

** Society of Plastic Engineers ratings. These ratings are based on irritation scores only. No consideration is given to potential sensitization or carcinogenic hazards.

SHELL CHEMICAL COMPANY

⑦

153
Other Shell
n-Butyl Glycidyl
Ether

DATE JANUARY 14, 1975

TO WOODBURY - P & RTC - SHELL DEVELOPMENT -
(H. FRANK)FROM MANAGER - TOXICOLOGY &
APPLIED PHARMACOLOGY -
SAN RAMONSUBJECT PRIMARY SKIN IRRITATION TESTS
WITH SEVERAL LOTS OF N-BUTYL
GLYCIDYL ETHER

Per your requests, TAP has conducted skin irritation tests with the following two lots of n-Butyl Glycidyl Ether:

Lot No. 06NHE2 and Lot No. 10THE10

Because of your specific request for a 4-hour observation time, the protocol that we would normally follow was modified to include a reading at the end of this period of time. The patches and wrappings were then replaced and readings made at the usual times of 24 and 72 hours.

The results of these two studies were compared with those of another lot number of n-Butyl Glycidyl Ether that we had tested for you in the past, and a copy of that report (Hine Report No. 51) is also included for your easy reference. (Note the difference in the scoring in Report No. 51, as compared to Reports No. 58 and 59.)

At the end of the 24-hour application period and the 72-hour observation period, I can detect little real difference between the three materials, when one takes into account the differences in scoring ratings and the fact that the materials were not compared at the same time.

Lots 06NHE2 and 10THE10 showed significantly less irritation at the end of 4 hours than they did at the end of 24 hours' application.

The Draize scores at the end of the 4-hour exposure for both lots were on the order of 3, and certainly less than 4.

After you have had a chance to review these results, we would be pleased to explore with you the necessity for a 4-hours' exposure with a 24 and 72-hour observation period, to satisfy the SPIC Code.

for *[Signature]*
M. B. Slomka

Attachments

cc: Woodbury - P & RTC - Shell Development (C. Uzelmaier) w/attach.
Houston - Supv. Reg. Affairs - Chemical Products w/attach.
San Ramon - I.S. (2) w/attach. ← THIS COPY FOR →

PRIMARY SKIN IRRITATION TEST OF n-Butyl Glycidyl Ether, Lot 06NHE2

A. Method: The backs of six New Zealand White rabbits were shaved from shoulder to flank on the day preceding application. Approximately 0.5 ml of the test material was applied to areas of intact and abraded skin. The spots were covered with Elastoplast coverlets and the rabbits were wrapped in elastic bandages. At 4 hours, the skin sites were uncovered and scored for irritation; the patches and wrappings were then replaced for an additional 20 hours. Readings were made again at 24 and 72 hours. The scoring method of Draize was followed each time.

B. Results: Individual skin irritation readings are presented in the table.

At 4 hours, there was negative to moderate irritation on intact skin and moderate to severe irritation on abraded skin, with no eschar present.

At 24 hours, there was moderate irritation on intact skin and severe irritation on abraded skin, with beginning eschar barely discernible in 2 of the rabbits.

At 72 hours, there was moderate to severe irritation on intact skin and severe irritation on abraded skin, with eschar present in 3 animals.

The primary irritation score was 4.2 which classifies the substance as severely irritating. (Escharotic for abraded skin.)

Primary Skin Irritation (24-Hour Exposure): n-Butyl Glycidyl Ether, Lot 06NHE2

Time of Exposure	Rabbit Number	Intact Skin		Abraded Skin		Score
		Erythema	Edema	Erythema (a)	Edema	
4 hours	1	0	0	0	2	1.0
	2	1	0	1	3	2.5
	3	0	0	2	2	2.0
	4	1	0	1	3	2.5
	5	2	2	2	3	4.5
	6	1	2	2	4	4.5
24 hours	1	1	1	3	2	3.5
	2	2	2	2	3	4.5
	3	2	2	3	3	5.0
	4	1	2	2	3	4.0
	5	2	2	3	3	5.0
	6	1	2	2	3	4.0
72 hours	1	2	1	4	2	4.5
	2	3	2	4	3	6.0
	3	3	2	3	3	5.5
	4	2	2	3	2	4.5
	5	2	3	2	4	5.5
	6	3	3	4	4	7.0

Primary Irritation Score: 4.2

Classification: Severely Irritating (Escharotic for abraded skin.)

(a) Readings of 4 under erythema: eschar

PRIMARY SKIN IRRITATION TEST OF n-Butyl Glycidyl Ether, Lot 10THE10

A. Method: The backs of six New Zealand White rabbits were shaved from shoulder to flank on the day preceding application. Approximately 0.5 ml of the test material was applied to areas of intact and abraded skin. The spots were covered with Elastoplast coverlets and the rabbits were wrapped in elastic bandages. At 4 hours, the skin sites were uncovered and scored for irritation; the patches and wrappings were then replaced for an additional 20 hours. Readings were made again at 24 and 72 hours. The scoring method of Draize was followed each time.

B. Results: Individual skin irritation readings are presented in the table.

At 4 hours, there was negative to moderate irritation on intact skin and moderate to severe irritation on abraded skin, with no eschar present.

At 24 hours, there was moderate irritation on intact skin and severe irritation on abraded skin, with beginning eschar barely discernible in 2 of the rabbits.

At 72 hours, there was slight to severe irritation on intact skin and severe irritation on abraded skin, with eschar present in 5 animals.

The primary irritation score was 4.3 which classifies the substance as severely irritating. (Escharotic for abraded skin.)

Primary Skin Irritation (24-Hour Exposure): n-Butyl Glycidyl Ether,
Lot 10THE10

Group of Singing	Rabbit Number	Intact Skin		Abraded Skin		Score
		Erythema	Edema	Erythema ^(a)	Edema	
rs	1	0	0	0	2	1.0
	2	1	0	1	4	3.0
	3	0	0	2	2	2.0
	4	1	1	2	4	4.0
	5	2	2	2	4	5.0
	6	1	1	2	3	3.5
rs	1	2	1	3	3	4.5
	2	2	2	3	4	5.5
	3	2	2	3	3	5.0
	4	1	2	2	3	4.0
	5	2	2	3	3	5.0
	6	1	2	2	3	4.0
rs	1	1	0	4	3	4.0
	2	2	2	4	3	5.5
	3	3	2	4	3	6.0
	4	2	1	2	2	3.5
	5	2	2	4	4	6.0
	6	3	2	4	3	6.0

Primary Irritation Score: 4.3

Classification: Severely Irritating (Escharotic for abraded skin.)

Readings of 4 under erythema: eschar

IRRITATION AND TOXICITY STUDIES OF N BUTYL GLYCIDAL ETHER

I. INTRODUCTION

A sample labeled 434-150-3 and identified as N butyl glycidal ether, CWLR-434-201 was received from Shell Development Company, Houston, Texas, at the request of Shell Chemical Company for primary skin and eye irritation tests.

New Zealand White male rabbits approximately 4 months old, weighing 2.5 - 3.0 kg were used for each test. They were acclimated in the laboratory at least one week prior to testing.

II. PRIMARY SKIN IRRITATION

- A. Method: The backs of six New Zealand White rabbits were shaved from shoulder to flank on the day preceding application. Approximately 0.5 ml of the undiluted test material was applied to areas of intact and abraded skin. The spots were covered with Elastoplast coverlets and the rabbits were wrapped in elastic bandages for 24 hours. Readings, according to the method of Draize, were made after this time and at 72 hours.
- B. Results: Individual skin irritation readings are presented in Table 1. The material produced eschar on the abraded skin of all six rabbits and on the intact skin of one rabbit. Due to the action of the liquid on the adhesive, removal of the tapes tore or abraded the skin and eschar formed in these areas, but intact skin - with the exception of the one rabbit - showed marked erythema and edema but no eschar. The primary irritation score (with eschar assigned a maximum score of 8) was 6.83 which classifies the material as severely irritating to escharotic.

III. EYE IRRITATION

- A. Method: One-tenth ml of the test material was instilled into the conjunctival sac of one eye of each of six New Zealand White rabbits. The eye was held closed for a few seconds and the animal was returned to its cage. Readings according to the method of Draize were made at 24, 48, and 72 hours.
- B. Results: Individual eye irritation readings are presented in Table 2. The material produced conjunctival irritation in all six rabbits and iritis and corneal effects in five. The corneal opacity was reversible in three to seven days. The average scores for 24, 48, and 72 hours were 28.8, 13.0, and 7.3 respectively, which classifies the material as extremely irritating.

Table 1 : Primary Skin Irritation: 434-150-3

Time of Reading	Rabbit Number	Intact Skin		Abraded Skin	
		Erythema	Edema	Erythema	Edema
24 Hours	1	2	1	eschar	
	2	3	2	4	3
	3	3	4	4	4
	4	3	2	4	3
	5	3	4	eschar	
	6	2	4	4	4
72 Hours	1	3	3	eschar	
	2	3	2	eschar	
	3	4	4	eschar	
	4	3	2	eschar	
	5	eschar		eschar	
	6	2	3	eschar	

Note: Tapes were extremely adherent due to solvent action on adhesive; skin was torn in areas upon removal.

Primary Irritation Score: 6.83

Classification: Severely Irritating to Escharotic

Table 2: Eye Irritation: 434-150-3

Time of Reading	Rabbit Number	Cornea		Iris	Conjunctiva			Score
		Opacity	Area		Redness	Chemosis	Discharge	
24 Hours	1	1	1	1	2	2	2	22
	2	1	3	1	2	2	2	32
	3	2	3	2	3	3	3	59
	4	0	0	0	1	1	1	6
	5	1	2	1	2	2	2	27
	6	1	1	1	3	3	3	28
Average								29.3
48 Hours	1	1	1	0	1	1	2	13
	2	1	1	0	1	1	2	13
	3	1	2	1	1	2	2	25
	4	0	0	0	1	1	1	6
	5	1	1	0	1	1	1	11
	6	0	0	0	1	2	2	10
Average								13.0
72 Hours	1	0	0	0	1	1	1	6
	2	1	1	0	1	1	2	13
	3	1	1	0	1	1	2	13
	4	0	0	0	1	1	0	4
	5	0	0	0	1	1	0	4
	6	0	0	0	1	1	0	4
Average								7.3

Classification: Extreme Irritation